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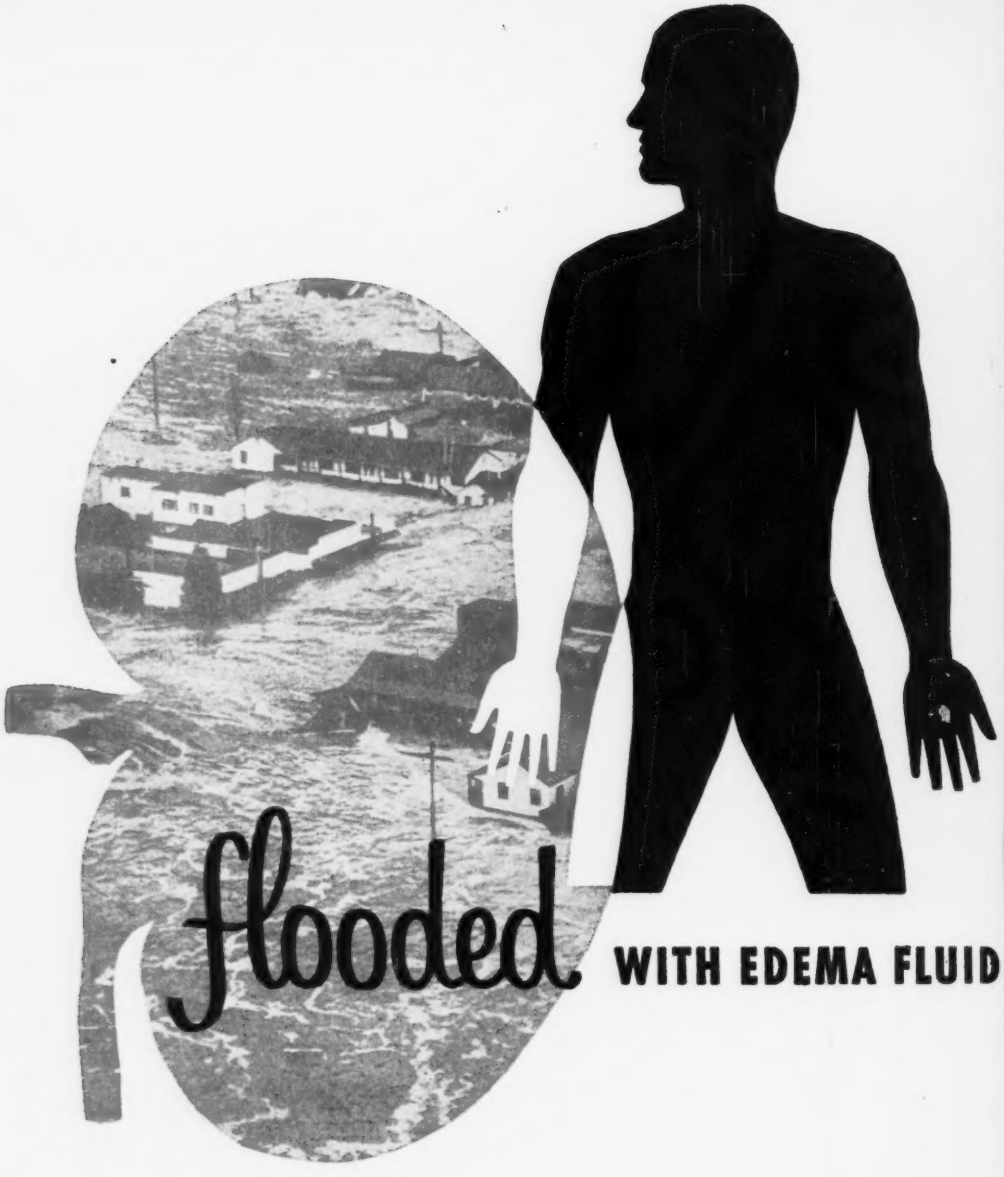

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Editorial

Ballistocardiography—Appraisal of Current Status

AN EXTRAORDINARY increase in knowledge of circulatory physiology has taken place relatively recently. This has largely been due to the introduction of improved methods for the accurate measurement of various hemodynamic events. There remains, however, an important gap that badly needs to be filled. There is no reliable method available for assessing the myocardial element of over-all cardiovascular function that is sufficiently simple to be applied to routine clinical practice. The need for this is most urgent in the management of patients with overt or incipient coronary artery disease. It is toward the goal of correcting this deficiency that much of the investigation in ballistocardiography is directed.

Several years ago an editorial prepared by us appeared[1] presenting an evaluation of ballistocardiography at that time. It pointed out that there were several serious objections to the adoption of the technic as a trustworthy tool in clinical practice. Three important objections were discussed and emphasized. The first of these was that conventional instruments supplied partially distorted and rather limited information about forces impressed on the body and that the new, improved instruments, which largely eliminated these differences, required more development to make them sufficiently practical and dependable for clinical utility. The second objection was that although empirical clinical correlations were of stimulating interest, they were not sufficiently complete to permit clinical conclusions from the records of an individual case. A final objection was that there were no controlled studies upon animals that demonstrated correlation between known hemodynamic events and ballistocardiograms.

The purpose of this editorial is to record what progress has been made over the intervening years. In our previous review it was stated that records obtained from the high frequency, low frequency, and direct body systems then in common use were greatly distorted and dominated by passive body oscillations that arose from a resonant coupling of the body and the structure supporting it. Since that time considerable progress has been made in the development of systems that lessen these important mechanical errors. It has been shown that the main source of artifact can be reduced or eliminated by the use of a supporting system that allows the body to move rather freely in space with minimal coupling to the earth. This was accomplished by several different methods, all of which for practical purposes, yield the same result. These methods are termed "ultra-low frequency systems," since the natural frequency of the body and support is extremely low. The methods are not really new, since the two earliest workers in ballistocardiography, Gordon in 1877 and Henderson in 1905, used systems of this sort. That the most important design characteristics arrived at intuitively by

The views expressed are those of a group working in ballistocardiography at the Johns Hopkins Medical School and Hospital consisting of: Drs. W. R. Scarborough, S. A. Talbot, F. W. Davis, Jr., R. E. Mason, M. L. Singewald, E. E. Folk III, B. M. Baker, Jr., and Mr. J. H. Condon.

This work is supported by research grants from the National Heart Institute, U. S. Public Health Service (H-327), from the Life Insurance Medical Research Fund, (#G-56-13), and from the U. S. Air Force.

these pioneers were physically sound has been established by recent analytical studies.

Whereas the waveform of the records from the older ballistocardiographic methods is significantly determined by passive body vibration, this is not true when the newer instruments are employed. As might be expected, these records are considerably different in waveform and contain meaningful information over a much wider frequency range. Records of the body's displacement, velocity, and acceleration have been obtained with various direct body methods, but the physical meaning of these records is obscure. However, displacement, velocity, and acceleration records from the ultra-low frequency systems have definite physical meaning.

Ballistocardiography is concerned, in the broadest sense, with measuring mass movements of the body in response to movements in the circulation and, by so doing, giving objective information about the over-all performance of the circulatory system. In this sense the term mass movements refers to movements not only of the mass of circulating blood but also of such masses as the heart itself during the cardiac cycle.

When the human body is supported in such a way that it in effect floats without restraint, then any motion of mass within that body will be reflected by oppositely directed motion of the body itself, so that the center of gravity of the whole system remains unchanged. If one records the displacement of the instrument's platform and the body it supports, with the onset of systole there is a headward displacement of the cardiovascular mass. This is followed shortly by a prolonged footward displacement that lasts until early diastole, after which there is a slow return in a headward direction until the beginning of the next beat. This agrees in general with what is known from physiologic studies by other methods regarding the direction and flow of blood in the arterial and venous systems during the cardiac cycle. Similarly, velocity records yield information about cardiovascular momentum (mass $\times$ velocity) since, ideally, cardiovascular mass times its velocity is equal to body mass times its velocity. Acceleration records, in like manner, yield information about cardiovascular force. Each of these types of records supplies a different and complementary kind of information about cardiovascular mechanical behavior. However, the fidelity with which these records reflect actual blood flow within the body has not been determined but is under active investigation.

Much of the recent biophysical effort in this field has been expended in attempting to extend the recording technic from the single longitudinal axis to other axes. Although lateral (or side-to-side) records have been obtained from conventional ultra-low frequency systems, these appear to contain a mixture of information, part of which is due to translation and part to body roll from rotation about the longitudinal axis. Evidence now available suggests that this sort of distortion can be eliminated only when the body is suspended so that it is free to roll, thereby yielding a roll-free lateral translational record.

Definite progress has been made in the development of suspensions of this kind but none is yet available for routine clinical use. There is good reason to believe that multidirectional recording will be as important in this field as it is in electrocardiography and in both cases frontal plane recording seems to be a minimum requirement.

The accumulated clinical work, most of which has been carried out with the classical instruments of Starr, Nickerson, and Dock, has yielded some stimulating clinical correlations. In general, the waveform of the ballistocardiogram is definitely abnormal in the majority of patients with overt cardiovascular disease although the frequency of abnormality is partially dependent on age. There has been hope that correlations between the type of cardiovascular disease and the kind of abnormal ballistocardiogram might reveal specific and characteristic record patterns of diagnostic value. These correlations have not been impressive, but probably no less impressive than those between anatomic diagnosis and other individual measurements of cardiovascular function. On the other hand, there is now reason to believe that this apparently limited specificity may have been due, at least in part, to

the fact that the cardiovascular information in the older ballistocardiograms was confused and distorted by meaningless artifact. The new instrumental methods will doubtless increase the specificity and precision of the measurements, but it is to be expected that records from them will correlate much better with functional than with anatomic circulatory conditions.

In addition to the interest that stems from these considerations, much of the effort in clinical ballistocardiography has been directed toward an evaluation of patients with coronary artery disease because other objective methods employed for the diagnosis and management of this condition are of limited value. It has been clearly established that the majority of patients with either angina pectoris or a history of myocardial infarction have abnormal ballistocardiograms at rest and in many of these there is no other objective evidence of cardiovascular disease. This would suggest that the method has real clinical value were it not for the fact that abnormal ballistocardiograms are found to occur in normal individuals above the age of 40 more and more frequently with increasing age. In the age range below 40 abnormal records from normal subjects are unusual but normal records from patients with coronary artery disease are common. Although it seems fair to assume that many older normal individuals have subclinical coronary artery disease, there is not yet proof that this is the cause of their frequently abnormal ballistocardiograms. At present these considerations limit the diagnostic value of ballistocardiography in coronary artery disease and make necessary a thorough search for supplementary procedures that will increase the separation between subjects with and without this circulatory abnormality.

In support of the belief that ballistocardiography measures some circulatory function of real clinical importance in patients with coronary artery disease, one observation in particular should be emphasized. There are well-documented instances in which ballistocardiographic waveform has been observed to deteriorate acutely during an attack of angina pectoris and to improve promptly when the attack was terminated.

Interest continues in the effect of cigarette smoking on the form of ballistocardiograms of subjects both with and without known coronary artery disease. A larger experience with this stress test bears out the earlier observation that it serves to separate patients from controls more impressively than does any other objective measurement. Ballistocardiograms of roughly one half the patients with overt disease deteriorate after smoking a cigarette whereas only 7 per cent of normal controls show such a response.

The data from clinical studies to date are too meager to permit definite conclusions upon the value of ballistocardiography in the clinic. Time may provide an answer as to whether there is prognostic significance to an abnormal ballistocardiogram especially now that there are newer methods of recording that may give more accurate information. The ultra-low frequency ballistocardiographic methods are so recent that data relative to their use are few. The American Heart Association's Committee on Ballistocardiographic Nomenclature, headed by Dr. Isaac Starr, recently published a recommended terminology for the several types of records from the ultra-low frequency systems. These new methods are now being explored by most of the research groups active in this field, but the only sizable clinical study yet reported appeared in an excellent monograph in Dutch by Elsbach, using the bed developed by Burger. Concentrating on younger individuals, he described characteristic or typical patterns in certain varieties of congenital and acquired cardiovascular diseases and showed that these could be correlated with specific hemodynamic alterations. This and similar work will in time undoubtedly demand revision of some of the previously held views that were based on results with the older methods.

Final confirmation or denial of the clinical value of ballistocardiography will almost surely come from a more precise understanding of its physiologic significance as a result of controlled experimental study upon animals. Experimental work in the human has been limited in the past and will probably remain so in the future because only the simplest and most innocuous procedures are ethically justified.

Animal work now in progress in several laboratories has moved slowly but now promises to make a significant contribution. The differences between man and the dog in body build, weight, flexibility, and other physical characteristics required the development of special ultra-low frequency ballistocardiographic beds and other suitable electromechanical instruments. The technical difficulties encountered in working with anesthetized animals proved much greater than those with cooperative, unanesthetized human beings. The necessity for controlling respiration, for making several physiologic measurements simultaneously and for performing open chest surgery made it still more difficult to obtain consistent and reproducible ballistocardiograms from dogs. Anesthesia alone produces deterioration of the waveform of ballistocardiograms from otherwise normal dogs, a fact that seems a tribute to the sensitivity of the technic in detecting changes in circulatory function known to result from anesthesia. Methods have been found for obtaining normal ballistocardiograms in anesthetized dogs both with and without artificial respiration over periods of many hours and these records are remarkably similar to those from normal human subjects.

This experimental work must be considered preliminary at present because experience has been limited. However, certain correlations between the ballistocardiogram and other mechanical aspects of normal and abnormal cardiovascular activity have already begun to emerge. The dynamic circulatory effects of normal and artificial respiration have been under investigation and interesting differences between unanesthetized man and anesthetized dog have been found. Other studies undertaken to assess the relative contributions to the ballistocardiogram of blood flow in the pulmonary and systemic circulations promise to yield important information. Attempts to separate the effects of motion of blood in the great vessels from motion of the heart itself on the ballistocardiogram have yielded inconclusive results; however, a definite relationship has been demonstrated between ballistocardiographic force and cardiac contractile or ejection force as measured by the strain gage.

A considerable amount of information may be expected from indirect experiments of this sort, but the ultimate hope in determining the physiologic origin and significance of the ballistocardiogram lies in the direct measurement of pulsatile blood flow in various parts of the circulatory system in the animal. Definite progress is being made in the development of flow meters suitable for this work, and there is reason to believe that these measurements will be possible in the not too distant future.

The instruments and procedures used in the field of ballistocardiography are of considerable technical complexity and the problems involved in providing the method with a sound physiologic basis will not be easy of solution. However, the promise this technic holds for providing information of a new and entirely different type about the mechanical function of the cardiovascular system demands continued and intensified research efforts. As complex as the method may be, one should not lose sight of the fact that from the patient's viewpoint it is a simple one, for the only thing required of him is that he rest quietly on a bed.

There is no denying the need for some objective method that will detect preclinical coronary artery disease. The hope for successful treatment by dietary, surgical, hormonal, chemical, and other measures makes this need an urgent one. It seems unlikely that an improved method suitable for routine clinical use will come from current research upon electrocardiographic, radiologic, and catheterization technics. Ballistocardiography is the only method now under study sufficiently simple from the patient's point of view that holds out some promise for evaluating over-all circulatory performance. In addition to what has already been said a preliminary observation leads us to believe that this can be accomplished. The ballistocardiograms of a small group of patients with overt coronary artery disease whose dietary fats were considerably restricted for a year or more improved in form significantly when contrasted with those of a control group allowed to select their diets freely. To our knowledge this observation provides the only

objective evidence indicating that dietary lipid restriction may improve circulatory function in human beings with coronary atherosclerosis.

This review is an expression of faith in the further development of ballistocardiography. A few years ago we took a strong position that many unjustified claims were being made for the clinical value of the method and since then we have consistently advised a conservative attitude. Partly because progress in this highly specialized and technically complex field has seemed slow, there has arisen recently some rather harsh criticism of the method that we think is unwarranted, especially as it now seems likely that current research will provide, within the near future, a sound physical and physiologic basis for ballistocardiography.

WILLIAM R. SCARBOROUGH
BENJAMIN M. BAKER

REFERENCE

1 HARVEY, A. McG.: Ballistocardiography. Am. J. Med. **17:** 295, 1954.

STOKES-ADAMS DISEASE

CHEYNE-STOKES RESPIRATION

Under these circumstances there was produced a group of symptoms and signs having a special character, namely, the combination of slow pulse, pseudo-apoplectic attacks, and murmur propagated into the aorta, while the second sound remained clear. In fact, my observations were based upon, and intended to illustrate, the views of Dr. Adams on fatty degeneration of the heart.

Cerebral symptoms, of a remarkable character, are commonly present in this disease. These consist in the occurrence of repeated pseudo-apoplectic attacks, of various degrees of intensity and duration. They are seldom followed by paralysis. Attacks of vertigo, dimness of vision, and syncope, are observed.

Sudden death, without rupture of the heart, or solution of continuity of the brain, is liable to occur in this disease.

A form of respiratory distress, peculiar to this affection, consisting of a period of apparently perfect apnoea, succeeded by feeble and short inspirations, which gradually increase in strength and depth until the respiratory act is carried to the highest pitch of which it seems capable, when the respirations, pursuing a descending scale, regularly diminish until the commencement of another apnoeal period. During the height of the paroxysm the vesicular murmur becomes intensely puerile.—WILLIAM STOKES. *The Diseases of the Heart and the Aorta.* Dublin, Hodges and Smith, 1854, p. 335–336.

Clinical Problems Related to Surgical Repair of Intracardiac Defects with the Aid of an Extracorporeal Pump-Oxygenator

By HOWARD B. BURCHELL, M.D.

The medical problems in the selection of patients for direct-vision reconstructive operations utilizing the pump-oxygenator of the Gibbon type are discussed. The evaluation of the pulmonary vascular changes is one of the most important medical tasks in many cases. The operative risk for such lesions as ventricular septal defect with high pulmonary flow, tetralogy of Fallot, pulmonary stenosis with intact ventricular septum, and atrial septal defect of the partial atrioventricular canal type is constantly decreasing and is 15 per cent or less at the present time. Heart block and cardiac arrhythmias are still, on occasion, serious postoperative complications. During 1 period of 3 months, subacute bacterial endocarditis (*Pseudomonas*) occurred in 4 patients but it has not recurred since.

IT IS an honor to have been asked to give the Henry Jackson Lecture this year. This invitation has afforded me the opportunity to correspond with his son, Henry Jackson, Jr., and hence to learn something of the interests of his father whose 82 years of life spanned the years of the development of the practice and teaching of scientific medicine in America. Henry Jackson came from a famous family of physicians and his first contribution to medical literature was in 1886 as "A Letter from Vienna," indicating one pattern of training of the best physicians at that time. He thereafter returned to Boston where he lived until 1940, dying then just at the dawn of surgical therapy of heart disease. One of his last communications was in 1933, 60 years after graduation, when he contributed to a symposium on the "Care of the Chronic Heart"—speaking on nonvalvular heart disease of middle and old age and emphasizing the important principles, particularly the ease and the error of making a poor prognosis in many cases. His son has mentioned that he possesses the original manuscript of this paper, with marginal notes containing the names of contemporary notables who had apparently been under his father's care.

The Henry Jackson Lecture at the meeting of the New England Cardiovascular Society, Boston, Massachusetts, May 14, 1957.

From the Mayo Clinic and the Mayo Foundation, Rochester, Minn. The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

The title of my lecture was suggested by your chairman, Dr. Dexter, and the data I shall present are related to surgical treatment primarily carried out by Dr. J. W. Kirklin but more recently also by Dr. F. H. Ellis, Jr., and the laboratory data have been made freely available to me by Dr. E. H. Wood. I am indebted also to numerous other clinical colleagues for their help with this paper, particularly Dr. J. W. DuShane of the Section of Pediatrics.

Perhaps it now would be a dull story to give you a detailed account of the development of cardiac bypass surgery initiated at our clinic approximately 5 years ago. However, few of us forget that first occasion on March 22, 1955, when the pump-oxygenator was used in the operating room—the interior of the heart of a little girl was exposed, a ventricular septal defect was repaired, and recovery ensued. At the present time, this child's heart is normal on physical examination. The artificial heart-lung apparatus, patterned after, but modified from, that developed for Dr. Gibbon, has continued to serve in a satisfactory way since that time.[1,2] Since August 1956, the heart has been stopped by potassium during the repair, as originally suggested by Melrose[3] and first done clinically by Effler.[4] It is proper to mention here also the pioneering and continuing stimulating surgical results with direct-vision cardiac surgery of Dr. Lillehei and associates.[5,6] In the approach to the problems of direct-vision cardiac surgery with the aid of a pump-

oxygenator, it might be well to review an index of a theoretical monograph, as follows.

1. Introduction—The Need.
2. Technical Problems of the Pump-oxygenator.
3. Technics of Intracardiac Repair.
4. Potassium Asystole.
5. Monitoring of Physiologic Variables during Operation.
6. Criteria for Cure—Varied Nature of Lesions Cured.
7. Pulmonary Hypertension as a Specific Problem.
8. Surgical Mortality.
9. Postoperative Complications.
10. Electrocardiographic Studies.

The specific problems introduced by the "bypass" have been many and varied. Their careful study in animals and in man has provided considerable knowledge of the proper management of whole-body perfusion. The importance of monitoring all the physiologic variables that we could monitor is that it gave us an understanding of basic principles at the time of the experimental work in animals and the early operations in man, and allowed us to discriminate and choose those measurements of promising perpetual value. The contributions of the laboratory of clinical pathology directed by Dr. T. B. Magath, aided by Dr. D. R. Mathieson, in blood grouping, cross matching, and collection of 7 to 10 bottles (500 ml. each) of heparinized blood the morning of operation have been one of the pillars in support of the surgical accomplishments.

To summarize from a clinical viewpoint, the present questions pertinent to bypass intracardiac surgery are as follows:

1. What is the risk of the extracorporeal pump-oxygenator per se?

2. What types of lesion may be cured and what are the specific surgical mortality rates?

3. When is palliative treatment (partial correction of a defect) warranted?

4. What are the evidences of "cure"?

5. What are the economic problems to patient and institution?

Some of these questions will be discussed later.

Diagnosis

It is not within the province of tonight's discussion to enter deeply into the intricate problems of diagnosis, but rather to summarize some general points that are pertinent to the surgeon's technical plans, to the immediate risks, and to the chances of a good result. In *many* instances we believe that on the basis of clinical data we can recommend surgical treatment without cardiac catheterization or angiocardiography, or both. If we can be reasonably certain that the patient has 2 ventricles and 2 great vessels, has no gross valvular defect, and has or has not arterial desaturation, dependent upon the presence or absence of pulmonary stenosis, he is potentially a surgical candidate. Even these simple criteria are not iron-clad guides for absolute exclusion of patients from surgical treatment; in a case of a single ventricle Dr. Kirklin has successfully placed an artificial ventricular septum in the heart of 1 patient, whose postoperative life was most satisfactory for 6 months, death then occurring suddenly with effort. Here is an instance in which a Bernheim effect could operate, I suppose, and if it should, it is an exceptional instance in the whole field of cardiologic problems where such an explanation for symptoms could pertain. Dr. Kirklin also was technically able to partition a truncus and do a reconstruction on the single truncus valve, separating it into 2, but the child in this instance survived only 24 hours. Anatomically this reconstruction appeared to have been soundly planned and executed and the ventricular septal defect completely closed.

One may well emphasize that despite our reliance on clinical diagnoses, cardiac catheterization is frequently performed when atypical clinical problems present themselves (and these atypical and complicated cases seem to be more and more frequently encountered). Cardiac catheterization data are valuable in some cases, for instance when special problems of hemodynamics need clarification, particularly when an objective value for pulmonary vascular resistance is needed; or in others, when an anomalous flow pattern needs delineation, as in anomalous pulmonary venous connections. The utilization of dye technics—the

sequential concentration of dye at a sampling site (for example, the radial artery) downstream from the injection site (for example, the pulmonary artery) as developed and applied in our laboratories under the direction of Dr. E. H. Wood—has been of great value in diagnosis.

It probably comes as no surprise to you to learn that the surgeon not uncommonly finds associated defects that were not suspected clinically or even sometimes on cardiac catheterization; an instance of this is that of atrial septal defects in association either with ventricular septal defects or with the tetralogy of Fallot. Also an occasional associated ductus has been encountered in patients in whom operations were scheduled only for repair of the ventricular septal defect. Of hemodynamic interest is the surgeon's observation, in a few cases, of the large size of the ventricular septal defect encountered when the hemodynamic data would have been indicative of a moderate-sized aperture only. With the opened, quiescent heart the surgeon has reported defects approximating the size of the aortic orifice when the moderately increased pressure in the pulmonary artery and the moderate left-to-right shunt logically would have been the basis for prediction of a moderate-sized defect. To me the only available explanation is that the defect must be decreased with systole (and that no significant left-to-right shunt is occurring during diastole). In 1 adult patient, the surgeon estimated the defect ("largest ever seen") as 5 by 2.5 cm., yet the aortic systolic pressure exceeded the right ventricular systolic by 15 mm. Hg. Preoperatively this patient had constant low values for her systemic blood pressure (80 to 85 mm. Hg systolic) and one might conjecture about this having had a benign influence on the pulmonary vasculature. The results of the surgical correction were good, with cardiac catheterization data 5 months later showing normal hemodynamics. The clinical recognition of valvular incompetence in association with septal defects has not always been easy in my experience. The association of aortic insufficiency with a ventricular septal defect represents a well-known syndrome, but fortunately a rare one; at present adequate repair of the prolapsed aortic leaflet would appear technically difficult. If the insufficiency is slight clinically, one does not have the grave concern of sending a child to operation, particularly since the previous potential difficulty of losing the perfusion retrogradely through the aortic orifice has been obviated by the use of potassium asystole and the cross clamping of the ascending aorta.

Of all the hemodynamic problems that engage the attention and the investigative potential of the physician in the field of selection of patients for surgical treatment, that of pulmonary hypertension has the highest priority. The essence of this challenging problem is that there are many patients whose heart can be repaired but whose pulmonary vessels cannot. Colloquially and slightly erroneously in a purely semantic sense, we speak of a lesion as "anatomically operable" but "physiologically inoperable." The inadequately or partly answered questions in this field of pulmonary hypertension in congenital heart disease associated with left-to-right shunts are: 1. How is structure related to pulmonary vascular resistance? 2. Is there any constant recession and secondary accession in the thickness of the vessels in the lungs from birth onward? 3. What is the genesis of the intimal lesions? 4. What retrogression may take place in the varied morphology of the thickened vessels and in the pulmonary hypertension following repair of a defect allowing a left-to-right shunt? 5. Can one identify a factor of dynamic resistance (vasomotion) and differentiate it from the structural resistance? 6. What would be the advantages of pulmonary biopsy in a patient with pulmonary hypertension in regard to the determination of operability and the prediction of postoperative recession in the pulmonary hypertension?

In the early work of Dr. J. E. Edwards and myself it was considered that the correlation between pulmonary pressure (and pulmonary vascular resistance) and pulmonary vascular morphology was a crude one. The extremes of pressure and vascular change could be seen to be related, but it was difficult or impossible to predict the extent of a left-to-right shunt, or to predict the weighting of a bidirectional shunt, in the presence of pulmonary blood pressure

equivalent or nearly equivalent to systemic blood pressure. Dr. Edwards[7] has proceeded to refine the categories of pulmonary vascular changes and has introduced the useful concept of the high-resistance, high-reserve, and the high-resistance, low-reserve lung, the term "reserve" being related to the capacity of the vessels of the lung to carry the flow of blood. A lung with low reserve is one in which there are advanced obstructive changes of the intima. Despite these advances, it is our belief that a study of vascular changes, as might be done by pulmonary biopsy, would not furnish a sound basis for determining operability, *if* this were already in grave doubt prior to this examination. As a special case in point, a child had a good result from closure of multiple ventricular septal defects, but died 4 months later from a hemorrhage of the subclavian artery. If a biopsy had been done, the vascular-bed vessels would have been assessed as severely obstructed, and with such a criterion for selection for operation it would have excluded the child from the successful surgical correction of the intracardiac defect. It is of note (and perhaps a little disappointing) that the pulmonary vasculature in this case showed no recognizable regression although pressure in the pulmonary artery was normal at the end of the repair.

Occasionally pulmonary biopsy will be of value. In one instance of a cyanotic young man, the pulmonary artery had not been entered on cardiac catheterization and although there was no characteristic accentuation of the second sound in the pulmonary area, the lung fields were of about normal vascularity and one was at a loss to know with certainty whether the patient had, with the demonstrated *right-to-left* shunt through a ventricular septal defect, a pulmonary stenosis or a severe pulmonary hypertension; in the former instance, operable; in the latter, nonoperable. Pulmonary biopsy was urged by Dr. D. C. McGoon, of the thoracic surgical team; it revealed thickening of the vessels that could only reflect severe pulmonary hypertension.

In patients with ventricular septal defects the main criterion for surgical treatment is the presence of a *left-to-right* shunt. The surgeon can repair this leak; surgical treatment is not mandatory if the leak is small due to a small orifice, but if the leak is small due to right ventricular hypertension and pulmonary vascular changes, surgical treatment is fraught with danger and the late results are not predictable at this time.

Electrocardiograms

Electrocardiographic studies are of inestimable help both in the differential diagnosis of intracardiac defects and in the estimation of the past and present hemodynamic states of patients having a ventricular septal defect. When the pulmonary fields are plethoric, patients who have a single ventricle or tricuspid atresia may simulate the patient with a simple ventricular septal defect, but the electrocardiogram may suggest the correct conditions. Patients with the atrioventricularis commune defect (common atrioventricular canal or so-called ostium primum defect) often have a characteristic electrocardiogram and vectorcardiogram. The left axis deviation in the standard leads and an apparent partial right bundle-branch block in the precordial leads are characteristic and are only very occasionally seen in a patient with an atrial or ventricular septal defect. Gross mitral incompetence is not necessary in the genesis of the nearly diagnostic tracing. In patients with ventricular septal defect one would like to demand evidence of left ventricular preponderance in the electrocardiogram if operation is to be recommended, but one cannot use the electrocardiogram as an infallible guide to operability, in my opinion. In this regard, while I am enthusiastic concerning the electrocardiogram as an index of operability for patients with ventricular septal defect, it cannot stand alone as an interdiction of surgical treatment if it should show predominant *right* ventricular hypertrophy.

Following surgical repair of a ventricular septal defect, either as an isolated lesion or as a component of the tetralogy of Fallot, it is expected that a right bundle-branch block will probably have developed, and that this is of classic conformation (fig. 1). In patients with defects of the ventricular septum in the muscular portion, one would not expect postoperative bundle-branch block and indeed this has hap-

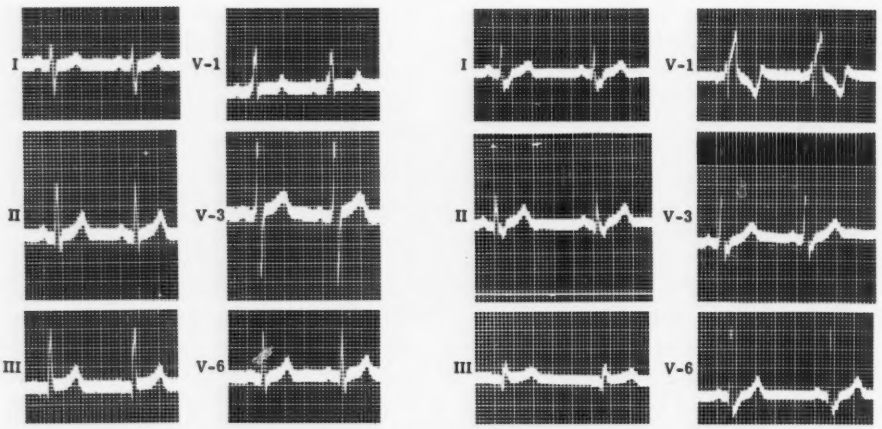

FIG. 1. Electrocardiograms from a young man before (*left*) and after (*right*) successful operation for pulmonary stenosis and a ventricular septal defect. The preoperative right ventricular systolic pressure averaged 90 mm. Hg, and a left-to-right shunt was present.

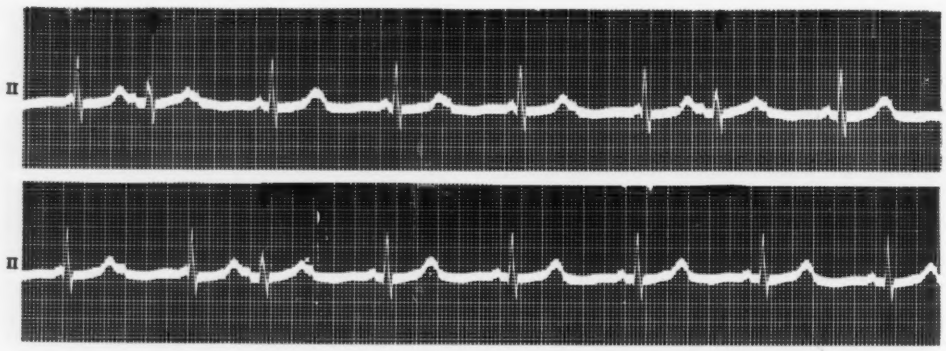

FIG. 2. Electrocardiograms taken on a girl, 19 years of age, 2 weeks after successful repair of tetralogy of Fallot. Complete heart block occurred postoperatively. The upper tracing shows interference dissociation, while the lower one shows an interference beat followed by 2:1 heart block. Arrows denote interference beats.

pened only once to date. When a patient has atrioventricular heart block, it is to be noted that only rarely, and then in the late hospitalization period, is there an increase in the P-R interval—atrioventricular conduction being in a normal range or no conduction occurring at all. In accordance with this conduction characteristic, one may often see sequences of 2:1 block followed by 1:1 conduction without difference in the P-R interval. Frequently, as a premonitory sign of resumption of normal sinus rhythm in a patient with heart block, one may see interference dissociation; that is, there may be a conducted beat if the P wave falls in a time-specific zone at the end of the T wave or the beginning of the U wave (fig. 2). This phenomenon is in accord with basic physiologic observations on the increased (or supranormal) conductivity during the late recovery period of injured excitable tissues; and in this instance of surgical injury to the junctional tissue of the heart, its manifestation is a welcome herald of the return of normal sinus mechanism. In patients with atrioventricular dissociation, the QRS configuration is usually that of *left* bundle-branch block, indicating that the most active tissue from the point of view of automaticity is in the right bundle area. As it is

expected that permanent right bundle-branch block is present, the possibility exists that complete heart block, when it occurs, is due to bilateral bundle-branch block and not necessarily to a lesion of the main bundle. In 1 patient, for a period just before resumption of normal atrioventricular conduction, there was retrograde (R-P period) conduction with the atria following the ventricular pacemaker and the QRS being of the left bundle-branch type. Following the repair of atrial septal defects, but not characteristically after other reconstructive intracardiac operations, nodal rhythm has been relatively common, usually at a moderately slow rate, and this has been of benign nature, perhaps even of salutary influence because of the control of the heart rate.

As yet, the full involution of the electrocardiogram to normal following surgical procedures has not been observed in patients, disregarding those having surgically induced right bundle-branch block, but one would expect a complete transition to normal to take some years if it is to occur at all. The electrocardiographic changes due to pericarditis following operation are unexpectedly minimal in most cases, in both the early and the late postoperative periods, and no residual electrocardiographic changes attributable to pericarditis have been seen.

One may mention that with the opened heart, there was the tempting opportunity to explore the pattern of excitation of the endocardium but such studies were deferred because of the possibility of increasing risk, and now with the almost universal utilization of potassium-created asystole, this electrocardiographic opportunity has vanished.

Postoperative Management

Before and after the surgical procedure, infants and children are weighed, and postoperatively they are brought to a recovery ward where they are under constant surveillance by experienced nurses. Special attention is paid to the drainage from either thoracic cavity, urinary flow, and any other loss of fluid, and the fluids are replaced as seems necessary on the basis of an accumulative chart with entries every 15 minutes for the first hour or so, then less frequently. The requirements for water (considered as 750 ml. per M.^{2} of body surface per 24 hours) are met, but no electrolytes are given for the first 2 days or more.

Dr. G. S. Sturtz, with Drs. Kirklin, E. C. Burke, and M. H. Power,[8] has studied various aspects of water metabolism in the first 3 days of the postoperative period in 21 patients who have undergone intracardiac operations with the aid of the extracorporeal pump-oxygenator. The weight of the child appeared to be the simplest guide to the requirements for water, but the studies on obligatory water losses were most informative in helping to arrive at a figure for probable water needs. The daily obligatory losses of water were considered as the obligatory urinary water (1 ml. of urine per mol of solute), insensible water loss, and the abnormal losses. The insensible water loss was assumed to be 90 per cent of insensible weight loss, according to the method of Newburgh. The daily water needs were considered as the obligatory water loss minus the metabolic water, assumed to be 270 ml. per M.^{2} of body surface per day. These calculations gave the water requirement as 500 ml. per square meter for the first day and 750 ml. per square meter for the second and third days. Of some interest is the finding that the serum concentration of water was low immediately after perfusion but returned to normal in 7 to 10 hours, and that it did not always conform to values expected from the water balance data. The data on the urine revealed that most patients in the first 36 hours excreted predominantly obligatory urinary water, which is believed strong evidence of an existing state of antidiuresis during this period.

Excessive bleeding has rarely been a problem and in only 2 patients did it seem that it was a serious hazard to recovery. The patients sometimes are in need of care because of severe hypotension in the early postoperative period, but this is uncommon in recent months. In such instances norepinephrine (Levophed) is still the drug that is favored and undoubtedly has been lifesaving in some instances.

The use of digitalis in our surgical cardiac cases has led to many discussions within our group, and I cannot claim exact scientific data to support our present practice utilizing this

valuable medication. Any patient who has, or has had, heart failure or who has atrial fibrillation receives full doses of digitalis preoperatively and maintenance doses following operation. Those infants and children who have had no digitalis preoperatively may receive it postoperatively on suspicion of heart failure. This practice is based primarily on the fact that some infants and children have developed heart failure postoperatively. In addition, there is supportive evidence for early use of digitalis from observations on the ease with which nonsurgical infants have developed heart failure with paroxsymal tachycardia. Adults who have not had digitalis prior to operation receive it postoperatively only as the need presents itself. A longer period of observation before its administration is warranted in adults as compared to children. In a few instances in which rapid arrhythmias have appeared postoperatively it has been most difficult to know whether digitalis had already been given in excess or the patient needed more. In one instance it was felt reasonably certain that the atrial tachycardia with varying heart block was related to digitalis. No response to the administration of potassium occurred, but there was alleviation by procaine amide, and recovery ensued without more digitalis being administered. In another instance late in the postoperative period a sinus tachycardia was associated with a 3:2 block with the Wenckebach phenomenon following the administration of only 2.5 mg. of digoxin in a period of 36 hours.

Complete heart block has continued to be an occasional, troublesome occurrence in the postoperative period in respect to its contribution to both morbidity and mortality. Transient atrioventricular dissociation as the patient's own heart takes over the circulation in the operating room is fairly frequent and not particularly worrisome, but if from the time of the operation heart block persists with an idioventricular rate less than 50 per minute, it is of ill omen as to survival. I had believed that if the ventricular rate was more than 60, with heart block, there would be no circulatory embarrassment; while this appears to be true, the prognosis must be guarded. To illustrate, in 1 child who had a satisfactory postoperative course with heart block with an idioventricular rate between 60 and 90, episodes of tachycardia developed on the ninth postoperative day with resumption of normal conduction, and the outlook was considered excellent for a normal sinus mechanism at the time of the approaching dismissal. The child died suddenly and unexpectedly, presumably of an arrhythmia. This patient was 1 of 2 dying in the late hospital period after episodes of arrhythmia; the second, however, did not have heart block. Heart block has appeared in 1 patient some hours after the surgical procedure and in this case it would be reasonable to attribute the block to edema or hemorrhage in the ventricular septum.

In complete heart block the utilization of the artificial pacemaker* as developed by Dr. Paul Zoll has been a boon to adequate management, and I believe lifesaving in a dramatic way in 2 patients: in 1, an adequate heart beat was maintained continuously for 4 days, and in the other for 8 days (fig. 3). The successful application of this technic lies not only in the excellence of the equipment but in the disciplined devotion to duty of the nurses and the resident surgical staff. The combination of the monitor and the pacemaker is such a valuable apparatus that I do not believe we could do without it. It may be mentioned that the automatic transfer to pacemaker by the monitor is not relied upon completely, as the attending physician is in a better position to utilize the pacemaker if he sees the rhythm mechanism and he may set the amplitude of stimulation and heart rate. If a rapid arrhythmia occurs during heart block, it is thought that the pacemaker's action would be voided or ineffective, and this is the explanation of the sudden death of an individual having episodes of tachycardia despite being connected to monitor and pacemaker.

Isoproterenol (Isuprel) has been a most valuable drug when the ventricular pacemaker begins to fail; it can be used rectally and sublingually as well as intravenously. In 1 child one quarter of an Isuprel linguet (2.5 mg.) every hour maintained an adequate ventricular

* Manufactured by Electrodyn Co., Norwood, Mass.

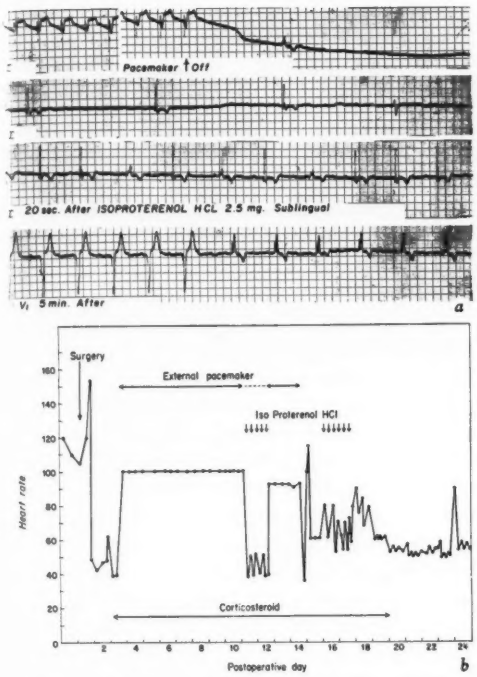

FIG. 3 *a*. Electrocardiograms in a 5-year-old girl 8 days after operation for ventricular septal defect and after use of an artificial pacemaker (Zoll) for 7 days. They show dependence of the ventricular beat upon the artificial pacemaker, but increase in rate of the ventricular pacemaker with administration of isoproterenol hydrochloride and the establishment of 3:1 heart block. Note change in QRS configuration from left bundle-branch form to right bundle-branch form when the idioventricular rhythm is replaced by conducted beats. *b*. Diagram illustrating the duration of time patient was maintained on the external pacemaker. At the time the graph ends the patient was maintaining a 2:1 heart block.

rate, that is, 50 to 80 per minute instead of less than 30 during many periods of several hours each.

When a potential catastrophe related to complete heart block is feared, I must admit that one does not wait for the dictates of scientific medicine to be formulated but may change, perhaps illogically, to a "do everything" philosophy, and may give the adrenal corticosteroids. I cannot report any unequivocal value despite the fact that the 2 patients who survived long periods of heart block were given these steroids. Molar solutions of sodium lactate have also been given on a number of occasions, but in the cases in which it was administered no change in the block was seen. Multiple observations on the effect of molar sodium lactate have been impossible because of the belief that an excessive sodium load would be detrimental to the general welfare of these patients shortly after the surgical procedure.

Of incidental interest is the fact that with one probable exception we have not observed any characteristic late postoperative syndromes such as associated pleurisy, pericarditis, and fever, which compose the typical postcommissurotomy syndrome.

Nature of Postoperative Deaths

When one of our patients has died after an operation in which extracorporeal circulation has been used, the postmortem examination—at least the discussion concerning claims and conjectures as to cause—persists long after the actual anatomic examination of the body. One must admit that the true mechanism of death is rarely established despite the close co-operative work of our section of pathology, particularly the efforts of Dr. Edwards, and that the valiant efforts of the clinical staff have resulted in no dearth of theories. A few conclusions concerning deaths are in order. In the first place, assuming the role of the sharpest critic, I have been unable to see definite evidence of a death being directly, only, and immediately attributable to perfusion by the artificial pump-oxygenator. In the early cases, deaths were not easily categorized etiologically, but with increasing experience the deaths early in the series can be reviewed and valuable lessons learned. 1. *Pulmonary complications* were distressingly common in the first 30 cases, but have now become relatively uncommon. This has resulted from careful attention to the ventilation of the lungs at operation, avoidance of hypervolemia, and precise surgical procedures. 2. *Apparently "sudden" deaths*, although seemingly mysterious, have been eliminated through the gradual perfection and refinement of technics, the use of excellent perfusion flow, and thus the avoidance of tissue anoxia and metabolic acidosis. 3. *Incomplete repairs*, especially in cases of ventricular septal defect and tetralogy, unquestionably

accounted for some deaths. 4. *Hypervolemia* was probably a factor in some cases. 5. *Heart block* has been an infrequent cause of death, but probably representing 8 per cent of deaths in recent months.

In deaths of patients with tetralogy of Fallot, the early convenient explanation for the death and the pulmonary edema often found was inadequate size of the left ventricle, but in the light of our total experience and the smooth postoperative course of some patients with this condition, such an easy explanation is hardly tenable.

The late postoperative deaths have been few but trying. Two patients with tetralogy of Fallot who underwent intracardiac reconstruction died of congestive heart failure after a few months. While postmortem examinations were not performed, it is accepted as most probable that these 2 patients, without cyanosis postoperatively, died because of an inadequately relieved pulmonary stenosis in the face of complete repair of the ventricular septal defect. No cases of this type have occurred recently, which is compatible with improvements in technics of relieving pulmonary stenosis to the extent of using a doubly pointed ovoid expansion patch on the outflow tract of the right ventricle and root of the pulmonary artery in some cases. Pulmonary valvular incompetence, if present after operation, was not expected to be a problem and so far, practically speaking, it has not proved to be. A few patients have shown mild transient signs of heart failure after repair of a simple ventricular septal defect. One case in which such failure was most perceptible was that of a child who had intermittent heart block following operation and from whom digitalis had been withheld. One adult patient with severe pulmonary stenosis and heart failure had recurrent thromboembolic complications and died 3½ months after operation from these complications.

In the period from last November to January we witnessed the distressing occurrence of bacterial endocarditis in 4 patients, with *Pseudomonas* as the infecting bacterium, which was resistant to the usual antibiotics. Polymyxin was not of definite value. Two patients died and a third has probably died by this time. Because of these, the sterilizing technics for the pump-oxygenator were altered to what would seem to be the most thorough methods possible, and it is hoped that this problem has been eliminated.

Mortality

In a field of endeavor changing as rapidly as that of direct-vision cardiac surgery and in view of the numerous problems presented by the variations in the defects attacked, mortality rates for the heterogeneous total group mean little. *At present*, the mortality rate from utilization of the pump-oxygenator to supply the body with a normal systemic flow up to an hour under conditions of bilateral thoracotomy can be assumed to be less than 5 per cent, I believe.

The most homogeneous group of cases are patients with a ventricular septal defect and a large pulmonary flow, and in this group, excluding infants, the mortality rate has been approximately 15 per cent. In the infants operated upon for ventricular septal defect, the mortality rate has been much higher in the past than at present. Although these were all very sick youngsters, the reason for advising operation at this age, the mortality rate was great enough in the fall of 1956 to cause us to revert to the "banding" operation on the pulmonary artery in these very small patients. Refinements in surgical and perfusion technics have resulted in the resumption of reparative operations in even these small infants, with a decline in mortality rate that is gratifying. To this date nearly 100 patients with ventricular septal defect have been operated upon.

In the group of patients with tetralogy of Fallot there is even greater lack of homogeneity in the clinical and laboratory picture, and the initial experience with surgical treatment was discouraging, but the mortality rate for a group of 38 patients operated on in 1956 and to May 1, 1957, has been 26 per cent. Of particular interest is 1 adult patient with pulmonary stenosis and intact septum who came with class IV heart failure, apparently in his last days of life, phenomenally having no murmur at times, with a cardiac index of 1.6 L. and a pulmonary valvular maximal gradient of 200 mm. Hg. He responded to medical therapy sufficiently to allow surgical treatment. With the use of the

pump-oxygenator to bypass the heart, the pulmonary valve was opened and the right ventricular pressure reduced to 40 mm. Hg. Remarkable improvement occurred.

Criteria for Cure

The majority of the patients who have survived operation are believed to be cured of their primary defects, and confidence in this regard is greater in the later patients than in the first dozen or so that were treated. We have not considered it justifiable to recatheterize routinely the hearts of many children during and after their convalescence from operation, but eventually over the years the plans are to collect the data such a procedure provides.

Evidence for the cure of the defect may be submitted as follows:

Direct. 1. The surgeon's critical appraisal of his repair following its conclusion. This has had more value since asystole has been used. 2. The pathologist's appraisal of the repair in the patients who have not survived. As nearly all the deaths occur early, it is difficult to assess what might have developed in the area of the healed defect, but this consideration aside, the results are anatomically good. In the early experience, 1 or 2 patients had multiple defects of the ventricular septum, and the surgeon had apparently overlooked 1 of them. Dr. Kirklin believes it fair to say that in the "beating heart era" about 15 to 20 per cent of the patients had repairs that were not anatomically perfect; with asystole a complete repair is nearly always possible in the hands of an experienced surgeon. 3. Normal dye curves and decreases in pulmonary artery pressure obtained in the operating room.

Indirect (*Clinical*). 1. Improvement in the child's strength, weight, and tolerance to exercise. 2. Absence of cyanosis or hypoxemia under conditions of exercise. 3. Decrease in heart size (and, in septal defects, the pulmonary vascular shadows).

Some of the children have a persistent systolic murmur after convalescence from repair of a ventricular septal defect, and many patients who have had surgical treatment for pulmonary stenosis have a systolic murmur and occasionally a soft diastolic one. It is a dramatic auscultatory effect when murmurs are absent after operation, but the persistence of a murmur of mild intensity is not considered as definite evidence of a persistent septal defect. In many of the patients who had severe pulmonary hypertension the second sound in the pulmonary area remains accentuated following repair of their ventricular septal defects, but this is hard or impossible to evaluate quantitatively as a sign of persistent pulmonary hypertension. In an infant, previously thin and disabled, ability to exercise normally, gain in weight, and replacement of tumultuous heart action and murmur by a quiet heart action are evidence of clinical cure. In a few it has been proved by catheterization that the hemodynamics are also normal (table 1). However, it will take some years to establish the degree of regression of the pulmonary vascular resistance in those patients in whom it was markedly elevated preoperatively and to establish the preoperative clinical and hemodynamic profiles of those patients who do, and those who do not, have a "complete cure" after closure of the intracardiac defect.

Table 1.—*Repair of Ventricular Septal Defect on August 25, 1955, in a Patient, Age 6 Years*

	4-9-54	11-28-56
Pulmonary pressure, mm. Hg	109/74	33/14
Flow, L./min	5.4	2.3
Systemic pressure, mm. Hg	122/67	113/87
Flow, L./min	—	2.3
O_2 saturation, %	92	97
Shunts, left-to-right	Large	0
Right-to-left	Small	0

The cardiac defects that have been cured by direct-vision intracardiac operations utilizing an extracorporeal pump-oxygenator include (1) ventricular septal defect, (2) atrial septal defect, (3) common atrioventricular canal (when mitral valve is adequate), (4) anomalous pulmonary venous connection with atypical atrial septal defect (superior vena cava syndrome), (5) complete anomalous pulmonary venous connection, (6) pulmonary stenosis—infundibular or valvular with intact ventricular septum or both, (7) tetralogy of Fallot, cyanotic and noncyanotic, (8) aortic sinus aneu-

rysm with rupture, with and without ventricular septal defect, (9) congenital aortic stenosis, and (10) combined subaortic and subpulmonary valvular stenosis.

Summary

The general problems of direct-vision intracardiac surgery utilizing the extracorporeal pump-oxygenator from the viewpoint of the cardiologist are those of proper selection of patients and the care of the patient in the postoperative state. The surgeons have advanced their technics until there are few remaining lesions that may not be regarded as eventualiy operable. The technics of extracorporeal circulation may be regarded as established and no longer on trial. The apparatus patterned after the pump-oxygenator designed for Dr. Gibbon has established its worth, adaptibility, and reliability in our clinic, and there is no reason to change to any other type at this time. Potassium asystole has worked out exceptionally well.

The mortality rate for surgical procedures in young infants has been distressingly high, but the general condition of these babies has been critical even before operation. It may be emphasized that there is reason to believe that rapid progress is being made both in regard to reduction in mortality and in regard to the certainty with which the defects are being adequately repaired. Complete heart block occasionally occurs, and medically we may not have adequate means to maintain an adequate ventricular rate. The artificial pacemaker of Zoll has been of great assistance in maintaining an adequate ventricular rate and life in some patients.

The problem of pulmonary vascular disease remains one of the most important, and many aspects of it are puzzling. The degree of regression of the obstructive changes in the pulmonary vascular system in surgically treated patients with pulmonary hypertension awaits some years of study, but there are promising signs of involution in some cases.

Summario in Interlingua

Ab le puncto de vista del cardiologo, le problemas general del chirurgia intracardiac a vision directe con le utilisation de un pumpa-oxygenator extra le corpore concerne le correcte selection del patientes e lor curatura durante le periodo postoperatori. Le chirurgos ha perfectionate lor technicas usque a un puncto ubi pauc lesiones remane que non pote esser considerate como potentialmente operabile. Le technicas del circulation extracorporee pote esser reguardate como establite e ultra lor stadio experimental. In nostre clinica, un apparatura construite secundo le modello disveloppate sub le direction de Dr. Gibbon ha demonstrate su valor, adaptabilitate, e regularitate de servicio, e il existe a iste tempore nulle ration pro transir a un altere typo. Le asystole a kalium ha functionate exceptionalmente ben.

Le mortalitate in interventiones chirurgic in juvene infantes ha essite discoragiantemente alte, sed le condition general de iste babys esseva critic mesmo ante le operation. Il es a signalar que nos ha rationes a creder que rapide avantiamentos es in progresso si ben con respecto al reduction del mortalitate como etiam con respecto al grado de certitude que on possede de haber reparate le defectos adequatemente. Il occurre casos de complete bloco cardiac, e il es probabilemente ver que como medicos nos non ha medios adequate pro mantener un satisfacente rapiditate ventricular. Le pacemaker artificial de Zoll ha essite de grande valor in mantener un adequate rapiditate ventricular e assi le vita de certe patientes.

Le problema del morbo pulmono-vascular remane un del plus importante, e multes de su aspectos es enigmatic. Le grado de regression del alterationes obstructive in le systema pulmono-vascular in chirurgicamente tractate patientes con hypertension pulmonar attende annos de studio, sed in certe casos il ha signos promittente de involution.

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Medical Eponyms

By Robert W. Buck, M.D.

Litten's Sign. Professor Moritz Litten (1845–1907) of Berlin reported "On the Movements of the Diaphragm Normally Visible on the Thorax with Each Respiration. A Physiological-clinical Observation" (*Ueber die normaliter bei jeder Respiration am Thorax sichtbaren Zwerchfellst bewegungen. Eine physiologisch-klinische Beobachtung*) in the *Deutsche medicinische Wochenshrif-* 18: 273–275 (March 31) 1892.

"I have observed that it is possible to see the movements of the diaphragm . . . on the thorax in all healthy men. The phenomenon takes the form of a wave motion which, beginning on both sides at the height of the sixth intercostal space, travels downward with maximum inspiration in the form of a straight line or shallow furrow (which makes an acute angle with the ribs) over several intercostal spaces, at times as far as the costal margin. With expiration it rises again over the same area."

A more detailed account of the phenomenon is given in the paper "The Diaphragm Phenomenon and Its Significance from the Physiological and Clinical Standpoint" (*Das "Zwerchfellphänomen" und seine Bedentung vom physiologischen und klinischen Standpunkte aus*) which appears in the *Verhandlungen des Congresses fur Innere Medicin* 13: 309–319, Wiesbaden, 1895.

"The patient to be studied is placed in a horizontal position . . . with his feet toward the window, while the examiner, standing three or four steps away with his back toward the window, observes him from an angle of about forty-five degrees. . . . We are convinced that in a dark room the phenomenon is only visible if a source of light is so placed that the beams strike the thorax from the direction of the feet at an acute angle with the thorax."

Water Metabolism after Cardiac Operations Involving a Gibbon-Type Pump-Oxygenator

I. Daily Water Metabolism, Obligatory Water Losses, and Requirements

By GEORGE S. STURTZ, JOHN W. KIRKLIN, EDMUND C. BURKE, AND MARSCHELLE H. POWER

Daily water metabolism of 21 patients was studied for 3 days after intracardiac surgery and whole-body perfusion. The average obligatory water losses of these patients were approximately 500, 750, and 750 ml. per M.^{2} of body surface per day on the first, second, and third postoperative day, respectively. A simple system, which combines knowledge of the estimated postoperative water requirement with the known daily change in body weight, was devised to manage accurately water metabolism after intracardiac surgery.

THE purpose of this investigation was the determination of the daily water metabolism, the daily obligatory water losses, and the daily water requirement in children subjected to cardiac operations involving extracorporeal circulation of blood through a Gibbon-type pump-oxygenator.

All components of daily water metabolism—water input, metabolic water,* urine output, insensible water loss, and abnormal losses such as those from thoracic-tube drainage and emesis—were determined. From these data the daily water balance was calculated.

However, our prime interest centered upon the measurement of the daily obligatory water losses, which were the obligatory urine water, the insensible water loss, and the abnormal losses. The obligatory water losses may be defined as those that occur at a constant rate irrespective of the body's state of hydration. Gamble,[2] in his studies of life-raft rations, emphasized the obligatory nature of the insensible water loss and the urine water loss; these losses occurred in thirsting and fasting subjects despite the body's need for water conservation. In the postoperative patient abnormal losses, such as those from thoracic-tube drainage and emesis, must be regarded as obligatory losses. The daily obligatory water losses together represent the amount that would be lost on a postoperative day if a patient received no water. Hence, we have assumed that the amount of the daily obligatory water losses (minus the metabolic water) is a reasonable estimate of water need on a given day in our postoperative patients.

Incidental to our main objectives was an evaluation of the concentration of water in the serum.[3-5] We wished to learn whether such an evaluation would offer a reliable method of determining the status of body water in our patients.

MATERIALS AND METHODS

Twenty-one children who underwent a cardiac operation were studied. Extracorporeal circulation by means of a Gibbon-type pump-oxygenator[6] was carried out in each case (table 1).

Anesthesia was induced in each patient with cyclopropane; tracheal intubation was carried out after the induction. During operation the patient was maintained at a light level of anesthesia with ether and oxygen. Preoperatively, each patient received a small dose of pentobarbital sodium (Nembutal), and morphine sulfate in a dose of 1.0 mg. per 10 pounds of body weight. Operation was carried out with the patient supine. Exposure was obtained through bilateral anterior thoracotomy. Potassium asystole was induced in 18 of the 21 patients.

All balance studies were carried out in the Domitilla Cardiovascular Unit of Saint Mary's Hospital.

From the Mayo Clinic and the Mayo Foundation, Rochester, Minn. The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

Abridgment of portion of thesis submitted by Dr. Sturtz to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Pediatrics.

* The term "metabolic water" includes the water of oxidation and the preformed water of catabolized protein, fat, and carbohydrate.[1]

TABLE 1.—*Data on the Twenty-One Children in this Study*

Case	Age (years)	Height (cm.)	Weight (Kg.)	Surface area, M.²	Anatomic diagnoses	Duration	
						Operation, (hr.:min.)	Perfusion (min.)
1	7	119	20.7	0.8	Ventricular septal defect	4:00	39
2	5	113	18.0	0.8	Persistent atrioventricular canal; mitral valve cleft	3:55	40
3	4	104	14.8	0.7	Atrial septal defect; pulmonary stenosis, valvular	3:40	33
4	11	142	33.8	1.2	Ventricular septal defect; subacute bacterial endocarditis, healed	3:45	19
5	14	163	45.2	1.5	Congenital aortic stenosis, valvular	4:30	37
6	12	145	36.6	1.2	Ventricular septal defect	3:35	21
7	3	92	13.7	0.6	Ventricular septal defect; pulmonary stenosis, infundibular	3:50	32
8	8	126	21.8	0.9	Ventricular septal defect; pulmonary stenosis, infundibular and valvular	4:10	44
9	4	91	11.6	0.5	Ventricular septal defect; atrial septal defect	4:00	35
10	3	102	13.3	0.6	Ventricular septal defect	3:45	32
11	5	102	13.5	0.6	Ventricular septal defect	3:10	28
12	5	102	12.1	0.6	Ventricular septal defect	2:05	28
13	13	142	24.9	1.0	Atrial septal defect; patent ductus arteriosus	5:00	21
14	13	168	37.0	1.4	Ventricular septal defect	4:40	46
15	6	122	18.7	0.8	Ventricular septal defect; pulmonary stenosis, infundibular and valvular	4:45	57
16	6	117	15.4	0.7	Ventricular septal defect	3:35	44
17	9	123	21.1	0.9	Atrial septal defect	3:25	22
18	9	124	22.6	0.9	Ventricular septal defect; pulmonary stenosis, infundibular and valvular	3:45	37
19	14	135	27.3	1.0	Atrial septal defect; pulmonary stenosis, infundibular and valvular	5:30	71
20	9	135	26.8	1.0	Ventricular septal defect; pulmonary stenosis, infundibular	4:15	47
21	14	140	24.8	1.0	Ventricular septal defect	4:45	61

The unit was staffed by graduate nurses, one of whom was in attendance at all times during the study of each patient.

Each patient was in an oxygen tent throughout the study. The tent was filled with water mist generated by 2 Mist O_2 Gen* units.

Each patient was studied for 72 hours from the start of the operation. The patient was covered by a sheet during the study period, and no clothing was worn. The room temperature was 75 to 78 F. The studies were conducted between October 1, 1956, and February 14, 1957. All children operated on during this period were studied and the data on each of them are included in this paper.

Each patient was weighed nude each morning of the study period. The first weight of each patient was obtained in the operating theater at the end of the operation. Appropriate deductions were made for thoracic catheters, urethral catheters, bandages, intravenous catheters and needles, and clamps used to occlude the catheters during weighing.

Body weights were determined on 2 scales, 1 in the operating theater and 1 in the cardiovascular unit. Each of these scales was accurate to within ±10 Gm.

Blood was drawn from each patient before and after extracorporeal circulation, and 4, 7, and 10 hours after the end of operation. We attempted to obtain a blood sample every 12 hours but this was not always feasible in these severely ill patients. The blood samples drawn during the first 2 days of each study were obtained from a catheter whose tip was in the inferior vena cava. Blood samples drawn on the third day of study were usually obtained from the superficial veins of the arm. Two milliliters of serum from each blood sample were used to determine the osmolarity by freezing-point depression with a Fiske osmometer.[7] The osmometer was calibrated with known molal solutions of sodium chloride; measurements of osmolarity† were thus expressed as equivalent to milliosmols of sodium chloride per 1,000 Gm. of water.

* Mist O_2 Gen, Mist Equipment Co., Oakland, Calif.

† The term in common usage "osmolarity" has been employed in this paper in preference to the more accurate term "osmolality."

Urine was collected by means of a retention catheter in the bladder, which was connected by plastic tubing to a glass bottle. The first urine-collection period was 11 hours, the second 7 hours, and the rest 6 hours each. In 4 cases all collections of urine were at intervals of 6 hours. The output of urine was measured at the end of each collection period in glass cylinders calibrated in 10-ml. increments. Two milliliters of urine from each collection period were used to determine osmolarity.

Stools occurred only twice in the 60 patient-days of study. On each occasion the amount passed was very small and its weight was estimated. Amounts of vomited material of less than 15 ml. were estimated. Larger volumes were measured.

Blood loss was replaced volumetrically throughout the postoperative period. A careful record was kept of the hourly blood loss and blood replacement; the cumulative balance was recorded hourly. Thus blood balance was accurately known during the period of study and proved not to be a factor in the water balance.

Thoracic-tube drainage was included in the abnormal losses only when it was serous and when it was not replaced with blood. No sweating was observed at any time during the study of any patient in this series; if sweating did occur, this loss is included in the insensible weight loss. Surface area was calculated from nomograms constructed from the equation of Du Bois and Du Bois.[8] All water-balance data in this paper are expressed in terms of 1 M.^{2} body surface per 24 hours.

The input of water was predominantly by the intravenous route. Only on rare occasions was a patient allowed any water by mouth during the course of the 72-hour study. All intravenously given fluid consisted of 5 per cent solution of dextrose in water; any fluid given orally was tap water. No electrolyte or solid food was given at any time to any patient during the course of study. The volume of intravenously administered fluid was measured by means of the scale on the side of the bottle. All fluid given was assumed to weigh 1 Gm. per ml. The first study period was usually 20 hours. The data of this period were corrected to 24 hours. There were 21 first-day studies, 20 second-day, and 19 third-day. One patient died 46 hours postoperatively. The urine collection of the third day of 1 patient was lost.

Calculations. The concentration of water in the serum or urine was calculated by dividing 1,000 ml. of water by the number of milliosmols (m-osm.) in the sample; the units of the answer were milliliters of water per milliosmol of solute.[5] The equation is thus

serum or urine water concentration

$$= 1{,}000 \text{ ml. } H_2O/\text{milliosmols.}$$

The total excretion of urine solute was calculated by multiplying the urine volume (ml.) by the urine osmolarity (m-osm./1,000 ml.). The equation is

urine volume (*ml.*)

$$\times \textit{ urine osmolarity } (\textit{m-osm./1,000 ml.})$$

$$= \textit{total urine-solute excretion } (\textit{m-osm.})$$

Obligatory urine water was calculated on the assumption that the average minimal concentration of water in the urine of a postoperative patient who does not have renal or endocrine disease is 1.0 ml. m-osm. of urine solute. This figure was selected since it represents the average minimal value in our group of patients (section *C* of figs. 1 to 10). Gamble found 0.7 ml./m-osm. as the obligatory urine water of patients who we maintained without fluid intake for 96 hours. We believe our figure is physiologically more appropriate in postoperative patients. The equation is

urine solute (*m-osm.*) $\times$ *1 ml./m-osm.*

$$= \textit{ml. of obligatory urine } H_2O.$$

The difference between the total volume and the obligatory volume of urine represents the free water in the urine.

In this study the volume of the urine was assumed to be identical with the volume of the water; no correction was made for solids in the urine. This introduced a small systematic error in the data.

The insensible weight loss was determined by the method of Newburgh and associates. The insensible water loss was assumed to be 90 per cent of the insensible weight loss.[9] The metabolic water was calculated for each day of study of 4 patients. This was achieved after the directions of Newburgh and associates.[1]

Results

Daily Water Metabolism (*Section F of figs. 1 to 10*). The input of water ranged between 440 and 1,620 ml. per M.^{2} per day. It was usually 600 to 900 ml. Water inputs greater than 1,000 ml. occurred generally on the third day of study in patients who were progressing satisfactorily (figs. 1, 4, 6–8). One patient (fig. 9) received 1,020 ml. per M.^{2} per day during the first day of study to facilitate the administration of norepinephrine.

Metabolic water was assumed[3] to be 270 ml. per M.^{2} per day, except for 4 patients for whom urinary nitrogen data were available. Calculation of metabolic water for these patients (12 periods) on the assumption that intravenously administered glucose represented carbohydrate burned, gave values rang-

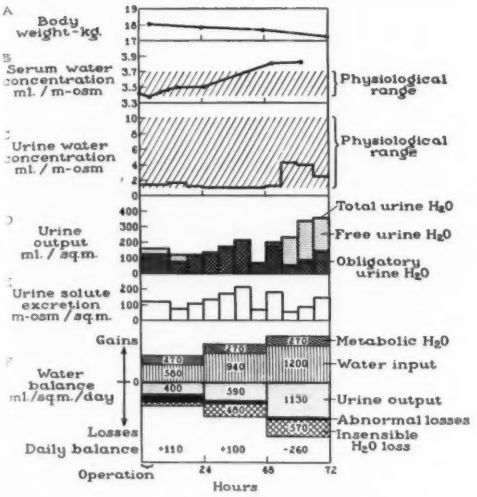

FIG. 1 (*case 2*). Note excess water input on the third day and the associated increased concentration of water in the serum and urine. Free urine water composed most of the third day's output of urine.

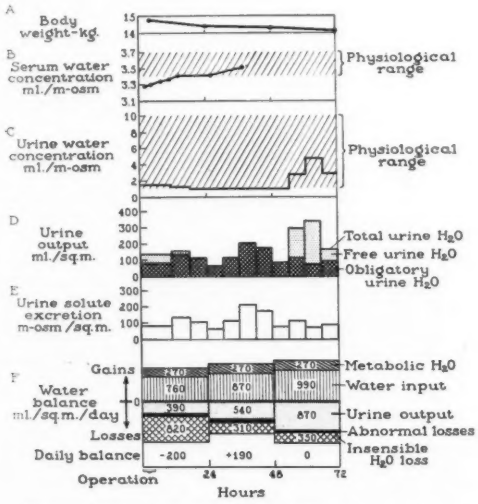

FIG. 2 (*case 3*). There were a large volume of urine, considerable free urine water, and an increased concentration of water in the urine during the last 24 hours of the study.

ing from 180 to 360 ml. per M.² per day; the mean was 279. Some of the individual values are included in figures 7 and 9.

The output of urine ranged from 110 to 1 170 ml. per M.² per day. During most days

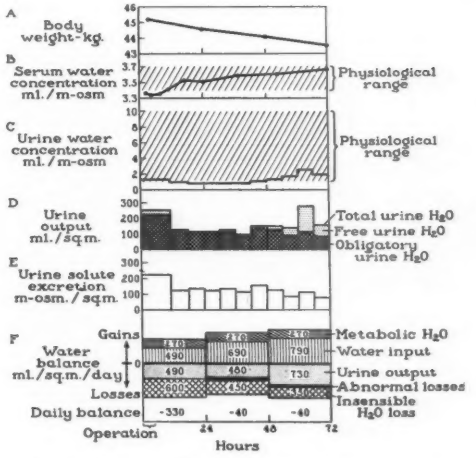

FIG. 3 (*case 5*). The serum water increased progressively although a negative water balance was present each day.

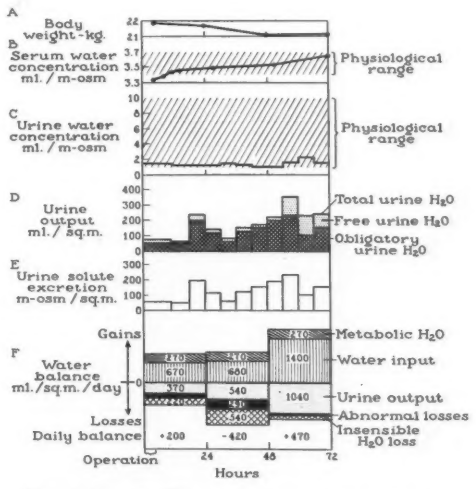

FIG. 4 (*case 8*). The water input was excessive on the third day. Positive water balance and a gain in body weight resulted since the renal excretion of water was insufficient to maintain zero water balance.

of study, the output was directly dependent on the amount of solute excreted (*D* and *E* of fig. 5). However, some patients who received a moderate water load had an increased volume of urine due to considerable free urine water on the third day of study (figs. 1–3).

The abnormal losses were generally small. On some days there were no abnormal losses.

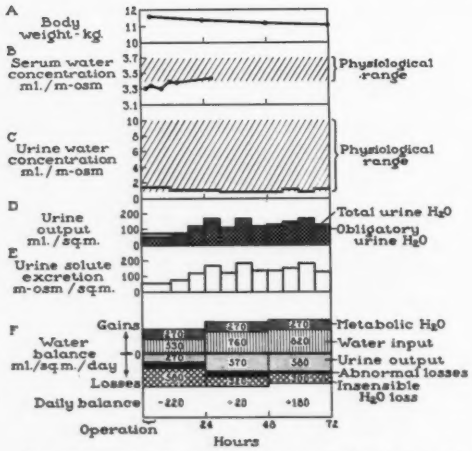

FIG. 5 (*case 9*). Water balance was maintained adequately throughout the study period. Note the low concentration of water in the urine and the almost complete absence of free urine water. The volume of urine was for the most part dependent on the amount of solute excreted.

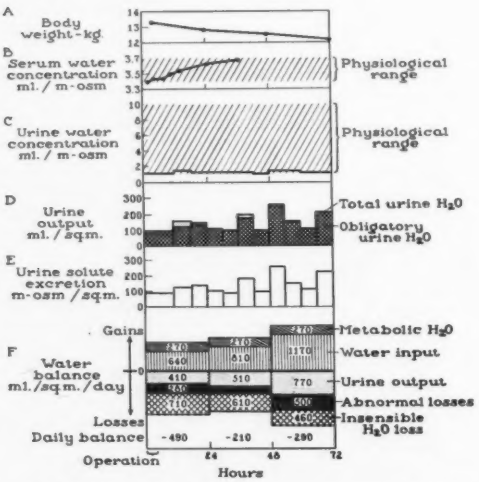

FIG. 6 (*case 10*). Although negative water balance was present on each day, the concentration of serum water rose progressively. The low concentration of urine water and the small amount of free urine water suggest nearly maximal conservation of renal water.

Occasionally these losses were quite large (figs. 6 and 8).

The mean value for insensible water loss was 469, 420, and 321 ml. per M.² per day on the first, second, and third day, respectively (table 2).

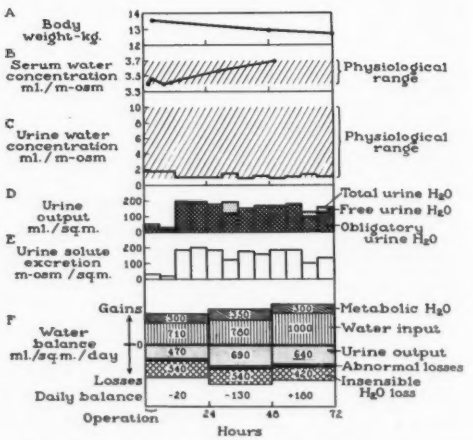

FIG. 7 (*case 11*). Note the small volume of urine during the first 12 hours of the study. During the first 48 hours of study the concentration of serum water rose steadily although the patient was in slightly negative water balance.

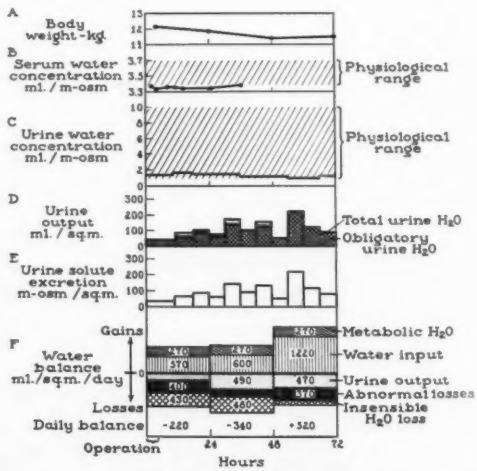

FIG. 8 (*case 12*). The concentration of serum water was low during the first 36 hours of study. Excessive water input on the third day resulted in positive water balance and a gain in body weight. The low concentration of urine water and the absence of free urine water on the third day suggest the presence of antidiuresis.

During 60 patient-days of study the calculated water balance ranged between a negative balance of 490 ml. per M.² per day and a positive balance of 570 ml. per M.² per day (section *F* of figs. 1 to 10; the patient with

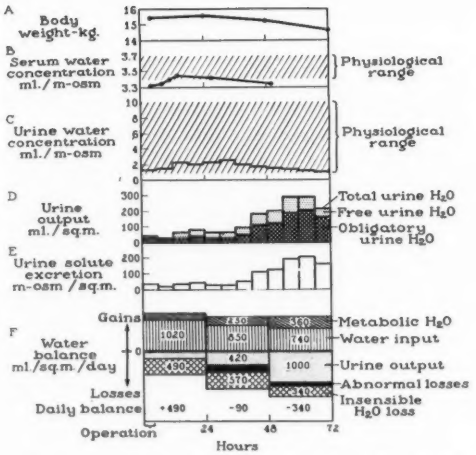

FIG. 9 (*case 16*). The large water input of the first day was used as a vehicle to administer levarterenol for the maintenance of the patient's blood pressure. Note the small volumes of urine during the first 42 hours. The urine of the third day was mostly obligatory to remove solute retained during the first 2 days. The low concentration of serum water at the fiftieth hour may have been related to the decreased renal excretion of solute.

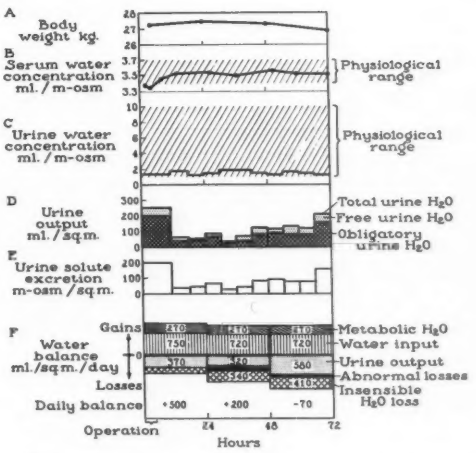

FIG. 10 (*case 19*). Although water input was approximately the same on each day, there was considerable variation in the daily losses. The concentration of serum water remained approximately constant after the first 12 hours while water balance varied considerably. This patient was perfused for 71 minutes.

positive balance of 570 ml. is not represented in the figures). There was a fair correlation between the calculated water balance and the water balance determined by daily body weights. Calculations suggested that body water was maintained within ±2 to 3 per cent of the previous day's status during most periods of study.

In the course of determining the insensible weight loss, the body weight of each patient was determined immediately after operation and each day thereafter. The body weight decreased during 55 of the 60 study periods. Most patients lost approximately 200 to 400 Gm. per M.² per day (section *A* of figs. 1 to 10). However, 5 patients were observed to gain weight during a study period, 4 of whom are represented (section *A* of figs. 4, 8–10), and water-balance calculations in each instance revealed that the patient was in positive water balance of approximately 500 ml. per M.² per day (section *F* of figs. 4, 8–10).

It was estimated during the calculation of metabolic water that the patients were catabolizing approximately 150 Gm. per M.² per day of body solids. Taking this factor into consideration, we were able to estimate the water balance by means of the daily change in body weight. For example, a patient who lost 400 Gm. per M.² per day was estimated to be in negative water balance of 250 Gm. per M.² per day, while a patient who gained 400 Gm. per M.² per day was estimated to be in positive water balance of 550 Gm. per M.² per day. Thus the water-balance data derived by determining the gains and losses of water (section *F* of figs. 1 to 10) were checked against the water-balance data derived by the daily change in body weight (section *A* of figs. 1 to 10). There was a fair correlation between these 2 estimates.

Daily Obligatory Water Losses. The mean value for urine-solute excretion was 294, 465, and 548 m-osm. per M.² per day on the first, second, and third postoperative day, respectively (table 3). Thus the mean value for obligatory urine water was 294, 465, and 548 ml. per M.² per day on the first, second, and third postoperative day, respectively.

The mean value for insensible water loss was 469, 420, and 321 ml. per M.² per day on

TABLE 2.—*Insensible Water Loss (Milliliters per Square Meter per Day)*

Case	Postoperative day		
	1	2	3
1	850	500	540
2	120	480	570
3	820	310	350
4	240	470	150
5	600	450	350
6	400	270	230
7	450	670	130
8	220	540	140
9	580	320	300
10	710	610	460
11	540	540	420
12	430	480	130
13	160	230	230
14	390	340	310
15	210	170	—
16	490	570	340
17	510	450	450
18	580	380	270
19	150	340	410
20	650	280	320
21	750	—	—
Mean	469 ± 49	420 ± 30	321 ± 31
Standard deviation	±224	±135	±133

TABLE 3.—*Excretion of Urine Solute (Milliosmols per Square Meter per Day)*

Case	Postoperative day		
	1	2	3
1	280	730	540
2	290	570	460
3	330	560	350
4	380	560	460
5	480	530	410
6	340	440	510
7	360	600	360
8	300	450	680
9	250	600	590
10	350	470	750
11	430	640	590
12	180	420	460
13	250	220	790
14	170	470	620
15	290	480	—
16	120	220	690
17	340	410	510
18	230	460	550
19	280	200	410
20	470	270	680
21	60	—	—
Mean	294 ± 23	465 ± 33	548 ± 30
Standard deviation	±106	±146	±130

the first, second, and third postoperative day, respectively (table 2).

The abnormal losses were small in most patients. However, we arbitrarily assumed them to be zero on the first postoperative day and 150 ml. per M.^{2} per day on the second and the third day. The reason for this assumption will be mentioned.

Daily Water Requirement. The problem of water requirement was approached by assuming that the daily obligatory water losses represented a reasonable starting point for estimating the amount of water needed. A simple equation was derived that the volume of daily water need equals the obligatory urine water plus the insensible water loss plus the abnormal losses minus the metabolic water (which is a gain in available body water). Thus, if V represents the volume of daily water need, OUW the obligatory urine water, IW the insensible water loss, AL the abnormal losses, and MW the metabolic water (water of oxidation and preformed tissue water), then

$$V = OUW + IW + AL - MW.$$

All the above symbols have as their units ml. per M.^{2} per day. The metabolic water was assumed to be 270 ml. per M.^{2} per day for each day of study.[3] The abnormal losses were arbitrarily assumed to be zero in the calculation of the first day's obligatory losses; this was done to aid in achieving slight negative water balance on this very important day. The abnormal losses were arbitrarily assumed to be 150 ml. per M.^{2} per day on the second and third days; this is a reasonable approximation of what was found in this group of patients.

Substituting into the formula the data of the first 24 hours yields:

$$V = OUW + IW + AL - MW$$

$$V = 294 + 469 + 0 - 270$$

$$V = 493 \text{ ml. per M.}^2 \text{ per day.}$$

It is thought that 500 ml. per M.^{2} per day represents a reasonable estimation of the amount of water patients similar to these would need in the first 24 postoperative hours to keep them near zero water balance, provided there were no abnormal losses. If abnormal losses do occur they will place the patient in negative water balance, which seems most desirable on this day.

Substituting into the formula the data of the twenty-fourth to the forty-eighth hour yields:

$$V = OUW + IW + AL - MW$$

$$V = 465 + 420 + 150 - 270$$

$$V = 765 \text{ ml. per } M.^2 \text{ per day.}$$

Substituting into the formula the data of the forty-eighth to the seventy-second hour yields:

$$V = OUW + IW + AL - MW$$

$$V = 548 + 321 + 150 - 270$$

$$V = 749 \text{ ml. per } M.^2 \text{ per day.}$$

We have rounded off the estimate of water needs to 750 ml. per M.^{2} per day for the second and third days. It is thought that this figure represents a reasonable estimation of the amount of water patients similar to these would need on the second and third postoperative days to keep them near zero water balance. The estimation of abnormal losses that were added to the calculations for the second and third days simplifies clinical management; it saves volumetric addition to the daily water input as abnormal losses occur.

Serum Water Concentration (*Section B of figs. 1 to 10*). The concentration of water in the serum was very low immediately after perfusion. It returned to normal within 12 hours in every case except 1. This phenomenon will be discussed in a subsequent paper.[10]

There was considerable variance between the balance data and the serum water concentration in certain patients. One patient was in negative water balance during each 24-hour period of study. Yet the water content of his serum rose gradually throughout the study (fig. 3). Another patient was in negative water balance for the study period as a whole; his serum water concentration rose steadily throughout the study. A patient who was in positive water balance during the first 48 hours of study showed little variability of his serum water content (fig. 10). A rise of serum water concentration to the upper physiologic limit was observed in a patient who was in marked negative balance throughout the study (fig. 6). A value at the upper physiologic limit was noted during the fiftieth hour of study in a patient who was in slight negative balance for the first 48 hours of study (fig. 7). An abnormally low value was found in 1 patient at the fiftieth hour of study; this patient was in positive water balance during the first 48 hours of study (fig. 9).

Since some patients exhibited increased serum water in the face of negative water balance, while others showed unchanged or even decreased serum water with positive water balance, it seems that serum water in this group of patients was not a reliable reflection of the status of body water.

Urine Water Concentration (*Section C of figs. 1 to 10*). The concentration of water in the urine of most patients remained close to 1.0 ml. per m-osm. during the first 36 hours of study (section *C* of fig. 5). It was slightly more than this value after the perfusion of some patients (fig. 7). No high values for urine water content were observed during the first 36 hours of study. Some patients who received a moderate water load on the third day of study had a rise in their urine water concentration (section *C* of figs. 1 and 2). A few patients (section *C* of figs. 9 and 10) had values for urine water content of more than 1.0 ml. per m-osm. throughout the study.

Discussion

Daily Water Metabolism. Some of our patients received a water input greater than 1,000 ml. per M.^{2} per day. This seems to be an excessive amount in light of our measurements of obligatory water losses and calculations of the daily water requirement. We no longer administer large amounts of water to such patients.

Although our calculations of metabolic water are in approximate agreement with previously published figures,[3] the many variables affecting this calculation suggest acceptance of the results with caution. The assumption of Newburgh and others that 25 per cent of total energy output is represented by vaporization of water was derived from data collected under controlled environmental conditions. In the humid atmosphere surrounding our patients, dissipation of heat by vaporization of water was probably somewhat less than that observed under conditions of lower humidity. Such being the case, our values for metabolic water are underestimations of unknown degree. These do not, however, seriously affect the final calculations of water balance.

The data on output of urine (section *D* of figs. 1 to 10) reveal that most patients in the first 36 hours of study excreted predominantly obligatory urine water, that is, urine with an osmolarity of approximately 1,000 m-osm. per L. and a specific gravity of 1.025. This is strong evidence of antidiuresis during this time. It appears that such patients would tolerate poorly a large water load during this time.

Thirst was a striking symptom in almost every child in this series. It was present in most patients, even those who were in positive water balance. It is felt that thirst is an unreliable symptom. Wynn's[11] observation of thirst among patients with water intoxication substantiates our observation.

Although our prime objective in this investigation was to determine the daily obligatory water losses, we found the daily change in body weight a very useful clinical means of assessing a patient's water balance. It is our opinion that the daily change of body weight was the simplest, the most nearly accurate, and the most informative method of evaluating water balance. As soon as a patient was weighed in the morning it was possible to determine the change in body weight from the previous day. By assuming that 150 Gm. per M.^{2} per day of body solids were catabolized it was possible to estimate immediately the water balance.

Daily Obligatory Water Losses. The daily obligatory urine water is determined by the amount of solute excreted. Previously reported

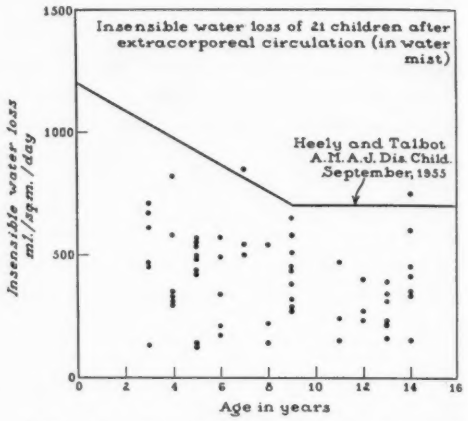

FIG. 11. Insensible water loss for all the 60 periods of study. Each dot represents 1 period of study.

data suggest that the excretion of urine solute is about 200 m-osm. per M.^{2} per day in patients receiving adequate amounts of water and dextrose.[3] Thus the much larger excretion by our patients seems unusual; it may be related to the surgical trauma or to the relief of heart failure. Our unpublished observations on children following other types of operation suggest that the increase in urine-solute excretion is probably a normal physiologic accompaniment of operation.

The mean value for insensible water loss for all periods of study was 406 ml. per M.^{2} per day. This figure is approximately 50 per cent of that reported by Heeley and Talbot[12] in their comprehensive study of hospitalized children. No single value greater than 850 ml. per M.^{2} per day was encountered in our 60 study periods (fig. 11).

Every patient was in an oxygen tent throughout the period of study; the tent was filled with water mist generated by 2 Mist O_2 Gen units. It is probable that the vapor pressure of the water in the tent was nearly 100 per cent saturated for the tent temperature. It is also probable that some particulate, liquid water generated by the 2 Mist O_2 Gen units was retained in the lungs. It is theoretically possible to block completely all pulmonary loss of water, or to gain water via the lungs, if the air is warm enough and the water vapor pressure is high enough. Thus it is thought that our data on

insensible water loss are not a measure of the water of vaporization alone; rather they reflect the loss of vaporized water minus the liquid, particulate water gained via the lungs.

One group of investigators decreased markedly the insensible weight loss of newborn infants by placing them in an "atmosphere supersaturated with water."[13] They were able to show that the decrease in insensible weight loss was due to a decrease in pulmonary water loss. Other investigators[14] showed that the insensible water loss decreased about 40 per cent when the relative humidity was raised from 20 per cent to 80 per cent. Both of these studies suggest that our low values for insensible water loss may have been the result of the large water content of the atmosphere within the oxygen tent.

Daily Water Requirement. It may be said that our estimations of daily water need are only mean values; therefore, the variability of the daily losses in this series suggests that one cannot achieve accurate water balance in any given patient. This statement is a truism. One cannot predict the daily losses in a particular patient before they occur. However, the use of a mean value is the best available method for estimating water need in a particular type of patient.

The use of the estimated daily water requirement together with the daily change in body weight makes accurate water balance possible in patients such as ours. For example, a patient may be noted to gain 200 Gm. per M.^{2} per day of body weight on the first postoperative day. Since approximately 150 Gm. per M.^{2} per day were lost by the catabolism of body solids and were replaced by water, it can be estimated that the patient was in positive water balance of approximately 350 ml. per M.^{2} per day. Knowing this, one would be inclined to give about 450 ml. per M.^{2} per day of water on the second day instead of 750 ml. per M.^{2} per day.

Or another patient may be noted to lose 1,000 Gm. per M.^{2} per day of body weight on the first postoperative day. Since approximately 150 Gm. per M.^{2} per day were lost as catabolized body solids, it can be estimated that the patient was in negative water balance of approximately 850 ml. per M.^{2} per day for the first day. This is 500 to 600 ml. per M.^{2} per day more than was desired. One should add 500 to 600 ml. per M.^{2} per day of water to the estimate of water need for the second day which is 750 ml. per M.^{2} per day. Thus, the amount of water would be 1,250 to 1,350 ml. per M.^{2} per day for the second day.

We have found that the technic of combining knowledge of the estimated water requirement with knowledge of the daily change in body weight is an invaluable aid in the daily management of water metabolism after cardiac operations involving extracorporeal circulation.

Summary

Various aspects of water metabolism were studied in 21 postoperative patients who had undergone intracardiac operations using extracorporeal circulation.

The body weight decreased daily in most of the patients. The usual weight loss was 200 to 400 Gm. per M.^{2} of body surface per day. The concentration of water in the serum was found to be low immediately after perfusion and it returned to normal in 7 to 10 hours. A disturbing lack of correlation between the serum water concentration and the water-balance data was noted. The concentration of water in the urine remained near its minimal value in the first 36 postoperative hours in most cases. It remained in this range during the final 36 hours except in these patients who received a moderate water load. Metabolic water was found to be 276 ml. per M.^{2} per day as a mean value for 12 study periods; this calculation is considered to represent an approximation only. The output of urine was almost entirely obligatory urine water except in a few patients who received a moderate water load on the third day of study. The obligatory urine water was 294, 463, and 548 ml. per M.^{2} per day on the first, second, and third day, respectively. The insensible water loss averaged 406 ml. per M.^{2} per day for 60 study periods. The small insensible water loss was presumed to be related to a decreased pulmonary water loss and possibly decreased skin evaporation.

A simple equation was derived to estimate the daily water need. The water input necessary to maintain balance was calculated to be

500, 750, and 750 ml. per M.² per day for the first, second, and third postoperative day, respectively.

It was considered that the body water was maintained within ±2 to 3 per cent of the previous day's status during most days of study.

Conclusions

Patients similar to ours can be maintained in water balance with 500, 750, and 750 ml. per M.² per day of water input on the first, second, and third postoperative day, respectively.

The daily change in body weight is the simplest, the most nearly accurate, and the most informative method of evaluating postoperative water balance. A decrease in body weight of 200 to 400 Gm. per M.² per day in the first few postoperative days appears to be the most desirable course. Provided the body weight is measured daily, it is possible to manage adequately water balance in the usual patient after extracorporeal circulation without such determinations as the concentration of water in the serum and urine, the excretion of urine solute, and insensible water loss.

The serum water concentration is of little value in assessing the postoperative water balance of patients undergoing intracardiac operations involving extracorporeal circulation.

The symptom of thirst is not reliable in patients such as these.

Acknowledgment

It is a pleasure to acknowledge the splendid cooperation given to us by Sister Maristella and the nurses of the cardiovascular unit, by Miss Lenore Rivers and Miss Catherine Ryan, and by Drs. William S. Lyons, Theodore T. Myre, Dwight C. McGoon, Manly B. Levin, and Richard A. Lim.

Summario in Interlingua

Varie aspectos del metabolismo de aqua esseva studiate in 21 patientes postoperatori qui habeva essite subjicite a operationes intracardiac con le utilisation de un circulation extracorporee.

Le peso corporee decresceva de die in die in le majoritate del patientes. Le usual perdita de peso esseva 200 a 400 g per m² de superficie corporee per die. Esseva trovate que le concentration de aqua in le sero esseva basse immediatemente post le perfusion e que illo retornava a valores normal in le curso de 7 a 10 horas. Esseva notate un disquietante absentia de correlation inter le concentration de aqua in le sero e le datos del balancia de aqua. Le concentration de aqua in le urina remaneva in le vicinitate de su nivello minimal durante le prime 36 horas post le operation in le majoritate del casos. Illo remaneva in iste mesme vicinitate durante le proxime 36 horas (i.e. usque al fin del periodo studiate), excepte in patientes qui recipeva un moderate carga de aqua. Esseva constatate que le aqua metabolic amontava a un valor medie de 276 ml per m² per die super le base de 12 periodos studiate, sed iste calculation es considerate solmente como un approximation. Le excretion de urina consisteva quasi completemente de aqua urinari obligatori, excepte in alicun patientes qui recipeva un moderate carga de aqua le tertie die del studio. Le aqua urinari obligatori amontava a 294, 463, e 548 ml per m² per die le prime, secunde, e tertie die, respectivemente. Le perdita insensibile de aqua amontava a un valor medie de 406 ml per m² per die super le base de 60 periodos studiate. Iste basse perdita insensibile de aqua esseva presumibilemente relationate a un reduction del perdita pulmonar de aqua e possibilemente etiam a un reduction del evaporation cutanee.

Esseva derivate un simple formula pro estimar le requirimento diurne de aqua. Le ingestion de aqua que es necessari pro mantener un balancia esseva calculate a 500, 750, e 750 ml per m² per die pro le prime, secunde, e tertie die postoperatori, respectivemente.

Esseva estimate que le aqua corporee esseva mantenite a intra ±2 a 3 pro cento del valores pro le ultime die ante le operation durante le majoritate del dies includite in le studio.

Es concludite que patientes simile a illes del presente reporto pote esser mantenite in balancia de aqua per medio de un ingestion de 500, 750, e 750 ml per m² per die le prime, secunde, e tertie die postoperatori, respectivemente.

Le alteration diurne del peso corporee es le plus simple, le plus approximativemente ac-

curate, e le plus illuminante methodo pro evalutar le balancia de aqua postoperatori. Un reduction del peso corporee per 200 a 400 g per m² per die durante le prime dies post le operation pare representar le plus desirabile curso. Si le peso corporee es constatate omne die, il es possibile regular de maniera adequate le balancia de aqua in le patiente usual emergente ab operationes con utilisation de circulation extracorporee, sin recurso a determinationes del concentration de aqua in le sero e le urina, del excretion de soluto urinari, del perdita insensibile de aqua, etc.

Le concentration de aqua in le sero es sin grande valor in le evalutation del balancia postoperatori de aqua in patientes subjicite a operationes intracardiac con le utilisation de un circulation extracorporee.

Le symptoma del sete non es digne de confidentia in patientes de iste genere.

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Water Metabolism after Cardiac Operations Involving a Gibbon-Type Pump-Oxygenator

II. Benign Forms of Water Loss

By GEORGE S. STURTZ, JOHN W. KIRKLIN, EDMUND C. BURKE, AND MARSCHELLE H. POWER

Each of 21 patients was noted to have a low concentration of water in the serum immediately after whole-body perfusion. This indicated a loss of water either by the patient or the pump-oxygenator. Investigation suggested that the patient, and not the pump-oxygenator, was the source of water loss. Two of the 21 patients had a profuse, short-lived solute diuresis in the immediate postperfusion period. These phenomena are apparently benign and they require no specific treatment.

DURING the study of a group of patients who had undergone cardiac operations involving whole-body perfusion, 2 unusual types of water loss were noted. One type, water loss during operation, was observed in each of the 21 patients. The other type, renal water loss, was observed in 2 of the 21 patients.

The materials, methods, and calculations used in this paper are similar to those employed in a preceding one.[1]

WATER LOSS DURING OPERATION

It was noted in each of the 21 patients studied that the concentration of water in the serum was very low after perfusion (fig. 1). Since the patients had no opportunity to gain solute during operation, it seemed likely that the low values for serum water content were due to rather sizable water losses during operation.

Accordingly, the Gibbon-type pump-oxygenator was investigated to see if it was a source of water loss. The machine was operated for 2 hours under conditions simulating the perfusion of a patient; blood samples were withdrawn from it every 15 minutes and the osmolarity of the serum was determined (fig. 2). The serum water concentration was calculated and it varied insignificantly during this 2-hour run. This study suggested that the pump-oxygenator was not an important source of water loss.

Next, the serum water concentration was determined at intervals during the course of operation in 1 patient (fig. 3). All samples were withdrawn from a catheter in the femoral artery. The patient received only a few milliliters of water during operation. Blood losses were recorded carefully and were replaced with equal volumes of blood. Figure 3 illustrates that the patient's serum water content was within the physiologic range at the onset of operation. It decreased steadily throughout the procedure. The figure also shows that the blood in the pump-oxygenator had a normal water content before perfusion, but that the content had fallen considerably at the end of perfusion. The steady decrease in serum water concentration during operation, but before perfusion, is strong evidence of a large water loss from the patient's plasma. This loss did not occur through the kidneys since the volume of urine during operation was small. Also the small volume of urine was offset by the small amount of dextrose in water solution given intravenously during operation. By exclusion, it seems reasonable to suggest that the water loss from the patient's plasma and the machine's plasma during operation was almost entirely insensible water loss.

Measurements of insensible water loss of postoperative patients similar to this one revealed a mean insensible water loss in the first 3

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Abridgment of portion of thesis submitted by Dr. Sturtz to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Pediatrics.

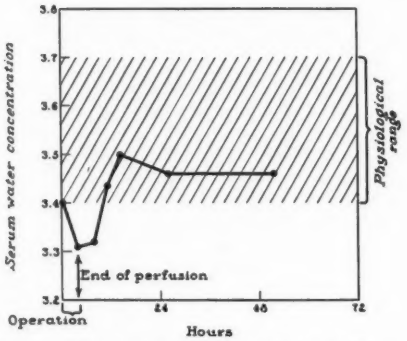

FIG. 1. The low concentration of water in the serum at the end of perfusion is evident. There was, however, a rapid return to the normal range 6 hours after perfusion while the water input was minimal. Concentration is in terms of milliliters of water per milliosmol of solute.

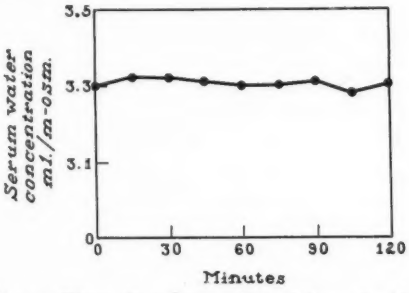

FIG. 2. These data were collected from the blood in a Gibbon-type pump-oxygenator during a 2-hour run under conditions simulating the perfusion of a patient. The steady water-solute ratio suggests that the pump-oxygenator is not an important source of water loss.

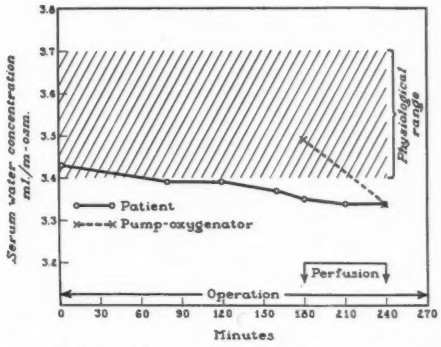

FIG. 3. The patient's serum water decreased steadily until the initiation of perfusion. The serum water of the patient and the pump were in equilibrium at the end of perfusion. Thus, the patient probably gained water from the pump's blood during perfusion.

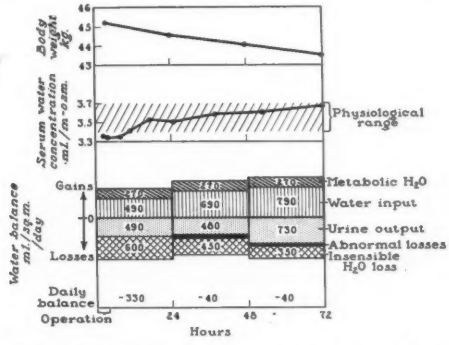

FIG. 4. The concentration of serum water returned to normal in 6 hours although the patient was in negative water balance.

postoperative days of 406 ml. per M.^{2} per day.[1] It appears that the insensible water loss (calculated as ml. per M.^{2} per 1 hour) during operation is much greater than that in the postoperative period. It is proposed that this greater insensible water loss during operation occurred predominantly from the moist, exposed pleural and pericardial surfaces while the usual insensible water loss via the skin was unchanged in amount.

Ruzic[2] subjected anesthetized dogs to a 2-hour abdominal operation during which he laid the small intestine out on sterile drapes and attempted to expose maximally to the air the mesentery and peritoneum. By weighing the dogs before and after operation he was able to estimate the insensible water loss; he found this loss to be 2 to 3 per cent of the body weight. His data and ours suggest that the moist serous surfaces within the thorax and abdominal cavities lose considerable amounts of water when exposed to room air.

The serum water concentration returned to the normal range in less than 12 hours in most cases (figs. 1 and 4). This occurred even in patients in striking negative water balance (fig. 4). In these cases, it appears that water from intracellular sources may become available to restore the serum water to more nearly normal levels.

No attempt was made to increase the amount of intravenous water during the first 24 post-

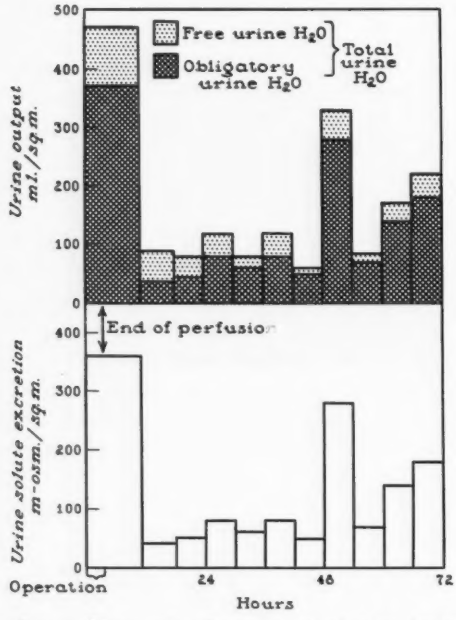

FIG. 5. There was a large output of urine during the first 11 hours of study. The urine contained a large amount of solute.

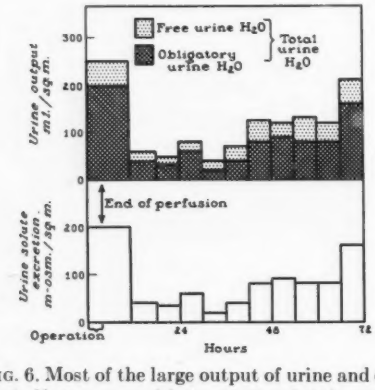

FIG. 6. Most of the large output of urine and excretion of solute occurred between 5 and 11 hours after perfusion.

operative hours in order to correct the low serum water content. It corrected itself in 20 of the 21 patients. We have come to regard this phenomenon of increased water loss during operation as benign, since no deleterious effects could be attributed to it. It is conceivable that this water loss might have been beneficial to these rather ill cardiac patients.

RENAL WATER LOSS

Two patients excreted large volumes of urine during the first 11 hours of study (figs. 5 and 6). In each instance most of this volume was excreted between 5 and 11 hours after the start of operation; this was 1 to 6 hours after perfusion. These specimens of urine consisted mostly of obligatory urine water. It might be said that a short, profuse solute diuresis occurred. Figures 5 and 6 show that each patient reverted to the usual pattern of excretion of urine water and solute after the eleventh hour of study.

SUMMARY

Data are presented which suggest that the insensible water loss was strikingly increased during cardiac operations involving extracorporeal circulation. It is believed that this loss occurred mostly from the exposed, moist pleural and pericardial surfaces. The Gibbon-type pump-oxygenator was not found to be a source of water loss.

Two cases are presented in which a short, profuse solute diuresis occurred in the immediate postperfusion period. The solute was accompanied by a large volume of water. This condition was short-lived. We regard these 2 phenomena as benign sequelae of this type of operation. No efforts were made to correct them and no untoward effects were observed.

SUMMARIO IN INTERLINGUA

Es presentate datos que suggere que le perdita insensibile de aqua es frappantemente augmentate durante operationes cardiac que utilisa un circulation extracorporee. Es opinate que iste perdita occurre principalmente ab le exponite e humide superficies pericardial e pleural. Non esseva trovate que le pumpa-oxygenator del type Gibbon es un causa de perdita de aqua.

Es presentate duo casos in que un breve profuse diurese de soluto occurreva durante le periodo immediatemente postperfusional. L

soluto esseva accompaniate de un grande volumine de aqua. Iste condition esseva de breve duration. Nos considera iste duo phenomenos como benigne sequellas del typo de operation hic considerate. Esseva facite nulle effortio a corriger los, e nulle effectos adverse esseva notate.

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THE STETHOSCOPE SONG

By OLIVER WENDELL HOLMES

There was a young man in Boston town,
He bought him a stethoscope nice and new,
All mounted and finished and polished down,
With an ivory cap and a stopper too.

It happened a spider within did crawl,
And spun him a web of ample size,
Wherein there chanced one day to fall
A couple of very imprudent flies.

The first was a bottle-fly, big and blue,
The second was smaller, and thin and long;
So there was a concert between the two,
Like an octave flute and a tavern gong.

Now being from Paris but recently,
This fine young man would show his skill;
And so they gave him, his hand to try,
A hospital patient extremely ill.

Some said that his *liver* was short of *bile*,
And some that his *heart* was over size,
While some kept arguing, all the while,
He was crammed with *tubercles* up to his eyes.

This fine young man then up stepped he,
And all the doctors made a pause;
Said he, The man must die, you see,
By the fifty-seventh of Louis's laws.

But since the case is a desperate one,
To explore his chest it may be well;
For if he should die and it were not done,
You know the *autopsy* would not tell.

Then out his stethoscope he took,
And on it placed his curious ear;
Mon Dieu! said he, with a knowing look,
Why, here is a sound that's mighty queer!

The *bourdonnement* is very clear,—
Amphoric buzzing, as I'm alive!
Five doctors took their turn to hear;
Amphoric buzzing, said all the five.

There's *empyema* beyond a doubt;
We'll plunge a *trocar* in his side.
The diagnosis was made out,—
They tapped the patient; so he died.

Now such as hate new-fashioned toys
Began to look extremely glum;
They said that rattles were made for boys,
And vowed that his buzzing was all a hum.

There was an old lady had long been sick,
And what was the matter none did know:
Her pulse was slow, though her tongue was quick;
To her this knowing youth must go.

So there the nice old lady sat,
With phials and boxes all in a row;
She asked the young doctor what he was at,
To thump her and tumble her ruffles so.

Now, when the stethoscope came out,
The flies began to buzz and whiz:
Oh ho! the matter is clear, no doubt;
An *aneurism* there plainly is.

• • •

Now, when the neighboring doctors found
A case so rare had been descried,
They every day her ribs did pound
In squads of twenty; so she died.

• • •

The poor young man was all aghast;
The price of stethoscopes came down;
And so he was reduced at last
To practise in a country town.

The doctors being very sore,
A stethoscope they did devise
That had a rammer to clear the bore,
With a knob at the end to kill the flies.

Now use your ears, all you that can,
But don't forget to mind your eyes,
Or you may be cheated, like this young man,
By a couple of silly, abnormal flies.

The Poetical Works of Oliver Wendell Holmes, Volume I. Boston and New York, Houghton, Mifflin and Company, The Riverside Press, Cambridge, 1904, p. 148–152.

Wolff-Parkinson-White Syndrome

Report of a Case Associated with Wandering Pacemaker, Atrial Tachycardia, Atrial Fibrillation, and Incomplete A-V Dissociation with Interference

By CHARLES FISCH, M.D., SHELDON T. PINSKY, M.D., AND J. PAUL SHIELDS, M.D.

It is the purpose of this communication to present a case of pre-excitation (Wolff-Parkinson-White syndrome) associated with various arrhythmias, some hitherto not described, and to stress the many features of this unusual case that support the bypass concept of the origin of this syndrome.

THE electrocardiographic pattern of short P-R interval and prolonged QRS with a normal P-S (Wolff-Parkinson-White syndrome, pre-excitation) has fascinated physicians since its description by Wolff, Parkinson, and White in 1930.[1] Many theories have been advanced and numerous studies reported in an effort to explain this particular electrocardiographic pattern.[2-4] Of the many concepts proposed, the 2 most widely accepted theories are the existence of an accessory pathway (bundle of Kent) and the presence of an irritable ventricular focus. It is not the purpose of this report to review either the concepts or the clinical significance of this syndrome, but to present a case that may have a bearing on the origin of W-P-W. This case has at one time or another manifested nearly all the hitherto reported disturbances of impulse formation and conduction complicating pre-excitation and, in addition, an arrhythmia that to our knowledge has previously not been observed with W-P-W.

CLINICAL HISTORY

The patient, a 58-year-old Negro woman was admitted to the Indianapolis General Hospital on April 27, 1956, with a history of progressive dyspnea first noticed in December 1955, followed by pedal edema, persistent cough, and extreme weakness. The patient apparently had been in good health and had required no medical attention prior to onset of present illness.

Examination on admission disclosed marked congestive failure, hypertension of 150/100–110, a regular tachycardia of 150, and marked cardiac enlargement. A mild hypochromic anemia, albuminuria, hematuria, a fixed specific gravity, and elevation of the blood urea nitrogen to 60 mg. per cent was also present.

The patient responded to treatment for congestive failure and the arrhythmias and was discharged on June 29, 1956. She was readmitted 3 times thereafter, however, because of generalized anasarca.

Description and Analysis of the Electrocardiograms

Figure 1A (*April 27, 1956*). This tracing was obtained before any medication was administered. The P-R interval is short (.08 second), the QRS prolonged (.12 second) with a distinct delta (Δ) wave on the upstroke, and the P-S interval measures .20 second. The S-T segment and T wave are opposite in direction to the QRS complex. A ventricular premature systole is present in lead I. The beginning of the R wave of this premature beat resembles very closely the delta wave of the other complexes. The findings here represent the Wolff-Parkinson-White syndrome with a ventricular premature systole.

The similarity of the first portion of the ascending limb of the ventricular premature beat to the delta wave suggests that the premature beat originates either near or in the bundle of Kent or in the irritable focus, depending on the concept of origin of W-P-W.

Figure 1B (*September 2, 1956*). This graph shows the normal pattern. P-R, QRS, and P-S measure .16, .08, and .24 second respectively. The T waves are inverted in leads I, aV_L and V_5.

Figure 2A. The 3 tracings (all lead I), each obtained on a different day, represent effect of

From the Robert Moore Heart Clinic, Indianapolis General Hospital, Indianapolis, Ind.

Supported by the Herman C. Krannert Fund of the Indiana Heart Foundation and the Indiana State Board of Health.

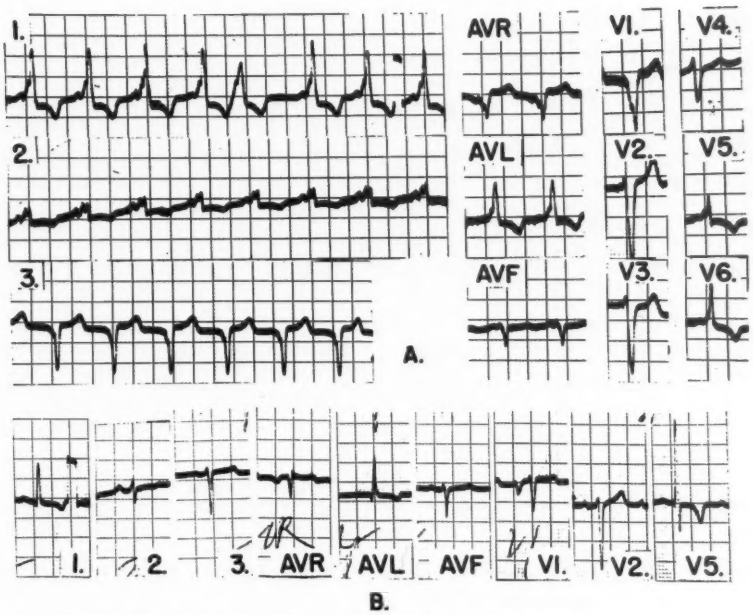

FIG. 1. *A*. Control tracings obtained on admission. Wolff-Parkinson-White syndrome with a ventricular premature systole. *B*. Normal conduction. The T waves are inverted in leads I, a V_L, and V_5.

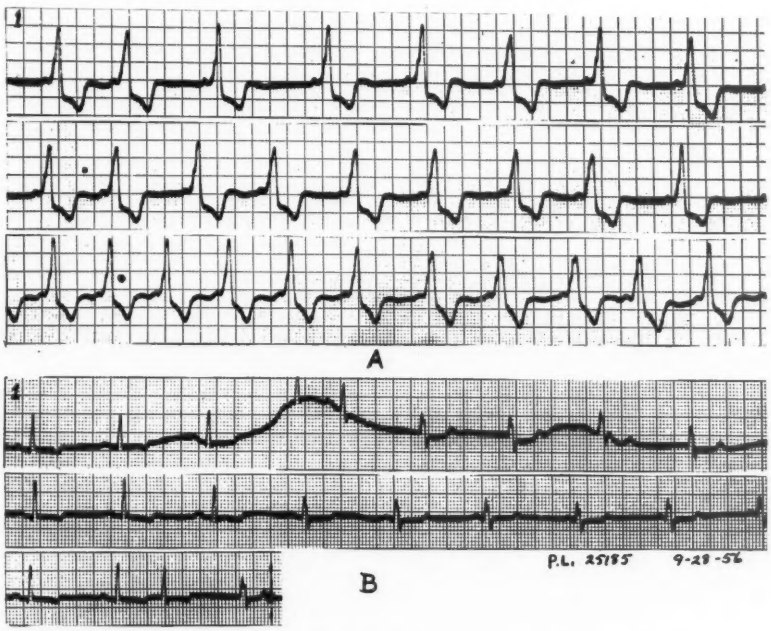

FIG. 2. *A*. Effect of vagal pressure on W-P-W. Note the change in rate and appearance of P and QRS waves. *B*. Lead I of a tracing with normal conduction showing appearance of idioventricular rhythm after vagal pressure.

vagal pressure on the W-P-W. In all 3 instances the heart rate slowed and the QRS contour changed. In the first and second strips, in addition to QRS alteration, 2 different P waves are present. The slightly taller, more pointed P wave is followed in each instance by a narrower and taller QRS (.14 second) complex with a P-S of .26 second. The shorter more rounded P wave is followed by a broader and lower QRS (.16 second) and P-S of .24 second. In the third strip only one type of P wave can be identified. Here the QRS shows gradual prolongation (.13 second to .16 second), the delta wave becomes more prominent, and P-S varies from .22–.26. The R-R intervals in the third tracing show a gradual change, while in the first 2 the variation of P wave is accompanied by a more abrupt change in R-R interval.

The change in contour of P wave and QRS complex can be easily explained by the well documented effects of vagal stimulation in the normal subject: (1) displacement of the pacemaker with change in appearance of the P wave, (2) delay of conduction at the AV node, (3) increase of rate of conduction through the AV node.[5] The displacement of pacemaker toward the node and acceleration of conduction via the node explains the "paradoxical" response observed in the first 2 strips, namely, that the vagal stimulation resulted in narrower and more normally appearing complexes. In the third tracing the delay in conduction via the node gave rise to the expected increase in aberrancy of the QRS complex, by allowing more of the ventricle to become activated by an abnormal route.

Figure 2B (*September 28, 1956*). This figure shows lead I of a normal tracing. In the upper strip, either coincidentally with vagal pressure or as a result of the latter, an atrial premature systole appears and is followed by sinus arrest and a series of aberrant ventricular complexes. Similar QRS complexes (also the result of a vagal pressure) appear in the second strip. These are preceded by normal P waves with a slightly changing P-R interval. The third and fourth beats of the middle tracing, however, represent fusion (combination) with the sinus beat. The lower tracings shows a spontaneous atrial premature systole with escape.

The first strip shows sinus arrest, atrioventricular dissociation, and an atrial premature beat with an escape beat. In each instance the subsidiary pacemaker results in identical QRS complexes. These QRS complexes could originate in (1) ectopic ventricular focus or (2) AV node (with aberrant conduction-preferential pathway). The differential diagnosis between the 2 would be difficult, if not impossible, were it not for the appearance of the fusion beats (beats 2, 3 in strip 2). These suggest strongly that the focus is in the ventricle and that we are dealing with an idioventricular rhythm. Furthermore, nodal beats without aberrant conduction are presented in figure 4*B*. Changes described here are pertinent to the interpretation of figure 6.

Figure 3 (*May 19, 1956*). This tracing shows parallel variation of heart rate and of the appearance of P and QRS. With abrupt slowing of the rate the P wave becomes more upright (except in V_4), the P-Δ longer, the QRS more normal (narrower, the delta wave forms a smaller portion of the ventricular complex) and the P-S shortens from .26 to .22 second.

When the P is associated with more normal QRS complexes, the P-S interval shortens (such a shortening of P-S was not observed in figure 2). The factors that resulted in slowing of heart rate in this instance not only displaced the pacemaker, perhaps toward the AV node, but also increased the conduction rate through the node. Such a displacement toward the node, and away from the bypass would explain the prolongation of the P-Δ interval. The relative prolongation of the P-Δ speaks very strongly against the irritable focus concept of W-P-W. There should be no reason for a delay in appearance of the delta wave if the latter resulted from mechanical stimulation of an irritable focus. The observation of similar changes during vagal stimulation (fig. 2*A*) suggests that the "spontaneous" changes in this instance may also be due to vagal effect.

Figure 4A (*May 12, 1956*). Lead V_1 shows atrial tachycardia with 1:1 response. The P-S cannot be determined. The QRS measures .14 to .16 second. The entire descending limb is thick and slurred.

Lead V_1 (May 10, 1956) discloses an atrial

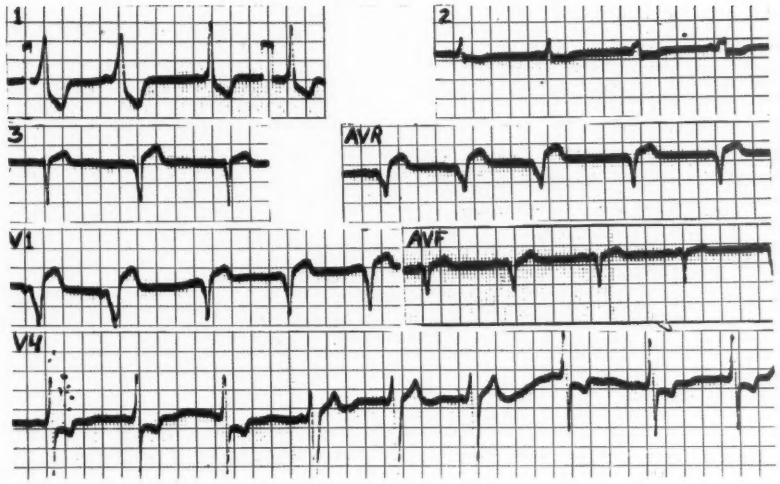

FIG. 3. This tracing shows parallel variation of heart rate and appearance of P and QRS. These changes occurred "spontaneously."

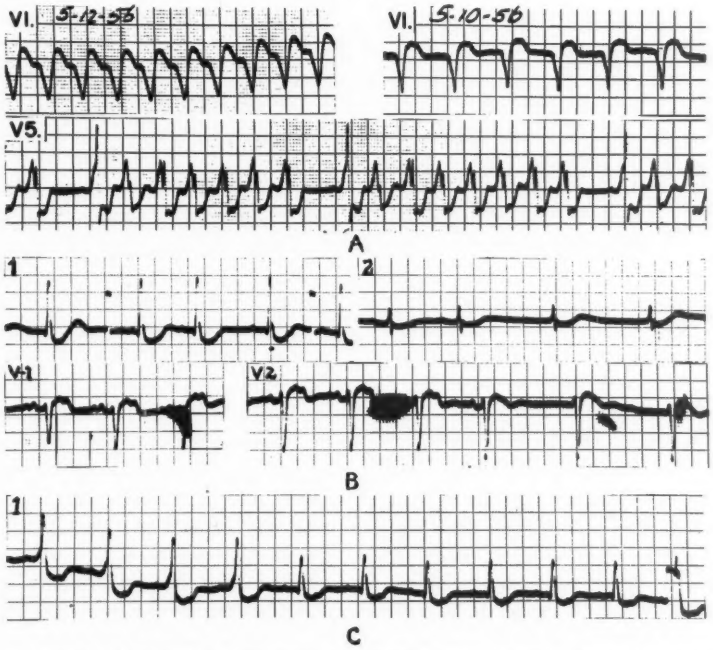

FIG. 4. *A*. Atrial tachycardia in presence of W-P-W. Left upper strip shows 1:1 response, while the right reveals a 2:1 response. Lead V_5 represents 1:1 response punctuated by cycles of 2:1 response. *B*. Atrial tachycardia with 2:1 response and normal atrioventricular conduction, atrial standstill, and nodal rhythm. Note the broad and notched P waves. *C*. Atrial tachycardia with 2:1 block showing transition from W-P-W to normal conduction.

tachycardia with an atrial rate of 180 and ventricular responses at 90 per minute. The delta wave occupies one-half the descending limb of the complex. The remainder of the QRS is slender and narrow and its entire width measures .12 second.

Lead V_5 (May 9, 1956) represents atrial tachycardia (rate 160) with a dominant 1:1 response punctuated by single cycles of 2:1 response. In the first QRS complex following a 2:1 response the ascending limb of the R is composed of an initially slurred (Δ wave) and a final narrow portion. The QRS complex measures .12 second and is of the RS type with a prominent S wave. Subsequent beats are of the RR′ type. The R wave is short with both limbs being slurred. The RR′ is narrow and the S wave is very shallow. The width of the QRS is .16 second.

That the arrhythmia is due to a rapid discharge from an ectopic focus, rather than a circus movement involving the bundle of Kent is suggested by (1) the P waves are not retrograde, (2) first beat of each cycle in lead V_5 shows the characteristic fusion complex, (3) some of the P waves are not followed by QRS complexes (it would be impossible to explain the subsequent P-QRS if one were to assume a circus movement via bypass and AV junction). These tracings also show a decided difference between refractory period of the bundle of Kent or the ventricular musculature as compared with the normal conduction path. When the ventricular rate is slow (V_1 with 2:1 response) and when the QRS follows a pause (first beat of each cycle in V_5), the QRS is narrow and represents a fusion with conduction through the node. When, however, the rate speeds up there is marked slurring and prolongation of the complex, indicating that most if not all of the ventricle is activated via bundle of Kent or from the irritable focus. That fusion is no longer present is indicated by the change in the terminal portion of the QRS complexes in V_5 with diminished depth of S wave. Furthermore, these beats are almost identical to those observed in figure 5 in which one can be quite sure that fusion does not exist.

Figure 4B (*May 15, 1956*). Atrial tachycardia with an atrial rate of 150 and 2:1 ventricular response. There are periods of atrial standstill with nodal rhythm. The P waves are peculiar in appearance, being broad (.16 second), notched, and upright in V_1 and V_2. They resemble to some extent the P waves observed in lead V_1 in figure 3. The P-R measures .22 second.

This tracing was taken after 1.5 Gm. of quinidine was administered in an 8-hour period. Although the dose was not excessive it could account for the return to normal of the QRS, marked prolongation of the P waves, and finally atrial standstill with nodal escape.

Figure 4C (*May 15, 1956*). Atrial tachycardia with an atrial rate of 160 and 2:1 response. The first 4 ventricular complexes are of the W-P-W type with a small P wave, a P-R of .12 second, and P-S of .28. Subsequent beats are normal. The terminal portion of both the W-P-W and normal complexes have the same appearance and the P-S remains constant, indicating fusion. It is significant to note that the P-Δ and P-R are longer than in any other tracing. Such a delay of ventricular activation speaks strongly against the irritable focus concept of W-P-W and in favor of a bypass.

Figure 5 (*May 15, 1956*). The dominant rhythm in this tracing is atrial fibrillation, and the ventricle is activated entirely through an aberrant pathway (fig. 6). Exceptions are the normal beats that occur after an interval of .80 second. Such long intervals preceding the normal beats suggest that the refractory period of the normal conduction tissue is longer than that of the aberrant pathway. The few beats with a W-P-W complex occurring after an R-R of .80 second can be easily explained by assuming that the bypass has been invaded by fibrillatory waves without invoking a ventricular response (concealed conduction). As a result, aberrant conduction after the longer R-R (.80 or longer) tends to give an erroneous impression of the refractory period of the bypass. In 1 instance a normal beat follows a normal QRS after a period of only .72 second. This beat may represent an attempt at an active nodal rhythm (nodal tachycardia). The burst of remarkably regular aberrant rhythm with a rate of 160 beats per minute suggests a mechanism other than atrial fibrillation. It may be that it repre-

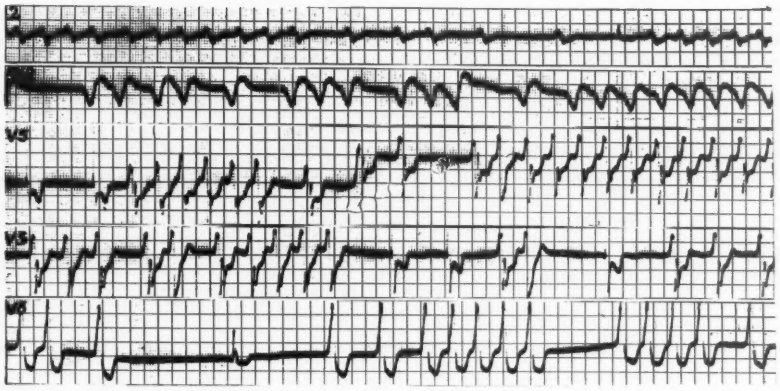

FIG. 5. Atrial fibrillation with W-P-W and normal atrioventricular conduction. Note the runs of extremely regular ventricular rhythm and the "double aberrancy" following prolonged R-R intervals (Ashman phenomenon). This is best seen in leads aV_R and V_5.

sents a tachycardia originating in or near the bypass. There are a few complexes that differ from both the dominant W-P-W and the normalized beats (e.g., beats 5 and 14 in fourth strip). These beats follow a prolonged R-R and represent aberrant conduction due to prolongation of the refractory period of the ventricles (Ashman phenomenon) superimposed on aberration secondary to W-P-W mechanism ("double aberrancy").

The lack of mechanical contraction of the atria and the presence of concealed conduction speak very strongly against the irritable focus concept of W-P-W. The appearance of W-P-W complexes after periods varying from .80 second to over 1.0 second cannot be easily explained except by concealed conduction. Such a mechanism is not applicable to the irritable focus concept. To accept the existence of an irritable focus, one has to assume that its threshold of response to stimulation varied markedly, thus resulting in wide variation of the R-R interval.

Figure 7 (*May 3, 1956*). The arrhythmia complicating W-P-W represented in this tracing has hitherto not been described. This tracing was obtained after 3.0 mg. of digitoxin was administered in 3 days and reveals a double tachycardia with an incomplete atrioventricular dissociation. At different times the ventricles are controlled by one or the other of the pacemakers. Occasionally impulses from both

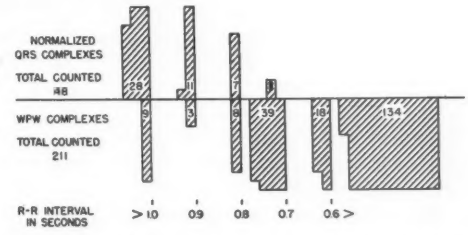

FIG. 6. This graph shows the R-R intervals obtained from the electrocardiograph of atrial fibrillation. A total of 259 intervals were measured and were divided into 2 groups: (1) R-R preceding a normal complex (48), (2) R-R preceding W-P-W complexes (211). Forty-six (96 per cent) of the 48 normal complexes appeared after an R-R of .80 second and only 20 (9 per cent) of the 211 W-P-W complexes were seen after an R-R of .80 second.

pacemakers invade the ventricle at the same time, giving rise to fusion (combination) beats. Two distinctly different (X, Y) and a number of intermediary (Z) QRS complexes are noted. The latter no doubt represent fusion (combination) between complexes X and Y.

The dominant rhythm is incomplete AV dissociation. The P-P intervals vary from .44 to .48 second and R-R interval from .40 to .44 second. The first of the Y complexes present in leads II, III, aV_L, V_1, and V_4 appear earlier than the dominant QRS (X) would be expected (after an interval of only .32 second). It represents invasion (capture) of ventricle by a supraventricular impulse. It is obvious when

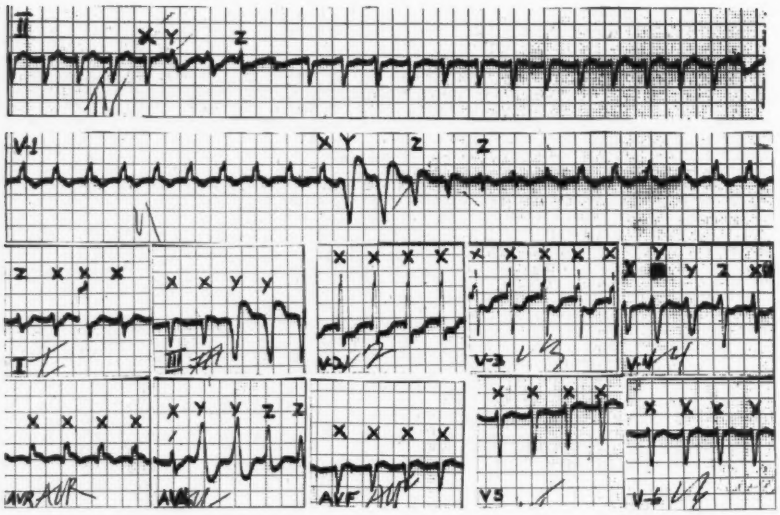

FIG. 7. Incomplete atrioventricular dissociation with periods of activation of ventricles through the bypass. Note the idioventricular (X) complexes, Wolff-Parkinson-White (Y) complexes and the combination of the two (Z).

compared with other tracings that the initial portion of the Y complexes is a delta wave and that the QRS pattern is the W-P-W type. The initial portion of the fusion beats (Z) is the delta wave and the terminal portion represents excitation from the ectopic focus. The 2 possible sites of ectopic pacemaker responsible for the X type of QRS are in the ventricular musculature and the AV node with aberrant conduction. Because the QRS (X) complexes resemble the idioventricular complexes in figure 2*B* and because nodal beats without aberrant conduction were present in figure 4*B*, we consider this ventricular rather than nodal tachycardia. If such is the case, it is difficult to accept the irritable focus concept as the origin of the W-P-W. For the latter to be true, one would have to postulate the existence of 2 competing ventricular pacemakers without any depression of either, as shown by the ability of a second ectopic pacemaker to respond within .32 second. Such a situation is highly unlikely. On the other hand, these findings are easily explained by the bypass concept. The aberrant path has a very short refractory period allowing early activation of the ventricles by this route. That the aberrant path has a refractory period that is shorter than the normal conduction pathway is also shown in figures 4*A* and 5.

SUMMARY

A case of Wolff-Parkinson-White syndrome (W-P-W) complicated by many different arrhythmias in a patient with severe heart disease is presented.

Several interesting features have a bearing on the etiology of W-P-W and some in our opinion strongly support the bypass concept: (1) incomplete AV dissociation with interference giving rise to W-P-W complexes, idioventricular complexes, and the combination of the two; (2) "double aberrancy;" (3) concealed conduction; (4) difference in refractory period of the 2 pathways resulting in changing appearance of QRS; (5) changing P-Δ interval; (6) variation in contour of P and QRS secondary to vagal stimulation or occurring "spontaneously" parallel with a change in heart rate; (7) findings that suggest that impulse can originate in the bypass without a preceding P wave and thus without evidence of mechanical stimulation; and (8) presence of W-P-W during atrial fibrillation where mechanical contraction of the atria is absent.

Acknowledgment

The authors are grateful for the cooperation and continuous support of Dr. Kenneth G. Kohlstaedt.

Summario in Interlingua

Es presentate un caso de syndrome Wolff-Parkinson-White in un patiente con sever morbo cardiac, complicate per numerose differente arrhythmias.

Plure interessante aspectos del caso es de interesse pro le etiologia del syndrome e in nostre opinion supporta fortemente le concepto del circumconduction. Iste aspectos es: (1) Incomplete dissociation atrio-ventricular con interferentia, resultante in complexos de Wolff-Parkinson-White, complexos idioventricular, e combinationes del duo; (2)"duple aberrantia"; (3) conduction celate; (4) differentias del periodo refractori del 2 vias, resultante in alterationes de QRS; (5) alteration del intervallo P-Δ; (6) variation de contorno in P e QRS, secundari a stimulation vagal o occurrente "spontaneemente" parallel a alterationes del frequentia cardiac; (7) constatationes que suggere que impulsos pote originar se in le circumconduction sin precedente undas P e assi sin evidente stimulation mechanic; e (8) presentia de complexos de Wolff-Parkinson-White durante le fibrillation atrial quando contraction mechanic del atrio es absente.

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A comparison of butter fat, corn oil, fish (sardine) oil and sunflower-seed oil was made. Fish oils contain little or no linoleic acid and only minute amounts of arachidonic acid. Sunflower-seed oil is a very rich source of linoleic acid and corn oil has a relatively high content. Fish oils are the most unsaturated of food fats. The mean total serum cholesterol level on the butter-fat diet was 52.0 mg. per 100 mg. higher than on the corn-oil diet, 35.8 mg. higher than on the sunflower-seed oil diet, and 39.8 mg. higher than on sardine-oil diet. These workers conclude that the serum cholesterol level does not bear a simple inverse relationship to either the content of "essential" fatty acids or the degree of unsaturation of the fatty acids in the diet.

McKusick

Raynaud's Disease Among Women and Girls

By Ray W. Gifford, Jr., M.D., and Edgar A. Hines, Jr., M.D.

The diagnosis of Raynaud's disease was suspected in 756 female patients at the Mayo Clinic from 1920 through 1945. The diagnosis was substantiated from the records of the initial examination or from the follow-up data or examination in 474. The clinical characteristics, including diagnostic criteria, clinical course, complications, and sequelae are discussed.

FROM January 1920 to December 1945, inclusive, Raynaud's disease, Raynaud's phenomenon, or questionable Raynaud's disease was diagnosed in 756 female patients at the Mayo Clinic. Data gleaned from a critical review of the clinical records and from follow-up questionnaires constitute the basis for the present report. In 1945 Hines and Christensen,[1] in a similar study of Raynaud's disease among men, reported that 77 per cent of patients with Raynaud's disease or Raynaud's phenomenon at the Mayo Clinic were women.

Diagnosis

Since Raynaud's original thesis,[2] terminology relating to Raynaud's phenomenon and Raynaud's disease has been confused. Raynaud's phenomenon may be defined "as an episode of constriction of the small arteries or arterioles of the extremities resulting in intermittent changes in color of the skin of the extremities, such as pallor, cyanosis or both."[3] Raynaud's phenomenon is, therefore, a symptom and not a disease. Raynaud's phenomenon may be associated with, and can be the first manifestation of numerous conditions or diseases, both local and systemic. When Raynaud's phenomenon is primary, that is, when it exists in the absence of conditions or diseases to which it may be secondary, it is properly called "Raynaud's disease." Allen and Brown[4, 5] re-emphasized and elaborated on Raynaud's original criteria for making a diagnosis of Raynaud's disease. Their criteria are: (1) episodes of Raynaud's phenomenon excited by cold or emotion; (2) bilaterality of Raynaud's phenomenon; (3) absence of gangrene, or, if present, its limitation to minimal grades of cutaneous gangrene; (4) absence of any other primary disease that may be causal, such as occlusive arterial disease, cervical rib, or organic disease of the nervous system; and (5) symptoms for at least 2 years.

Of the 756 girls and women in this series, 127 were promptly eliminated because the available information was inadequate, or the Raynaud phenomenon was obviously secondary to existing diseases. For the remaining 629 patients, the diagnoses as revised by the Allen-Brown criteria were then further validated or invalidated by follow-up information when available. Follow-up information was obtained by sending questionnaires to the patients and by re-examination at the clinic for some. The results are shown in tables 1 and 2.

From table 1 it is evident that adherence to the criteria of Allen and Brown led to a change in the original diagnosis in almost 30 per cent of the cases. There are two reasons for this: (1) many of the records antedated the publications of Allen and Brown[4, 5] in 1932 in which criteria for differentiation between Raynaud's phenomenon and Raynaud's disease were elucidated, and (2) the diagnosis of Raynaud's disease was changed unless the record clearly and unmistakably showed that all the criteria had been fulfilled.

Validity of Diagnosis Based on Allen-Brown Criteria. A diagnosis of Raynaud's disease according to the criteria of Allen and Brown was made for 377 of the 629 female patients by reviewing the initial records and was substantiated in 267 of 280 (95 per cent) by follow-up information. In 13 patients, diseases had developed in the interval to which the Raynaud's phenomenon may have been secondary.

Rheumatoid arthritis is believed to have

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developed in 5 of these 13 patients 2 or more years after the onset of Raynaud's phenomenon. Although the diagnosis of rheumatoid arthritis was unequivocally confirmed by examination at the clinic for only 1, it was strongly suspected on the basis of examinations at the clinic for 2 and on the basis of rather detailed follow-up letters from 2. The latent period between the onset of Raynaud's phenomenon and the appearance of rheumatoid arthritis varied from 4 to 14 years.

In 4 of the 13 patients acrosclerosis is believed to have developed 2 or more years after the onset of Raynaud's phenomenon. Three of these 4 patients had sclerodactylia (without other evidence of scleroderma) or trophic ulcerations of the fingers or both within 5 years of the onset of Raynaud's phenomenon, but acrosclerosis was diagnosed from 14 to 26 years after the onset of Raynaud's phenomenon. For the purposes of this paper sclerodactylia is defined as sclerodermatous changes confined to the skin of the digits. As a complication of Raynaud's disease it remains localized to the acral parts in contradistinction to the progressive scleroderma that is characteristic of acrosclerosis and diffuse scleroderma.

Two of the 13 patients who were thought to have Raynaud's disease by the criteria of Allen and Brown died of protracted febrile illnesses. One died at age 24 years 1 year after the apparently valid diagnosis of Raynaud's disease was made at the clinic, and 3 years after the onset of Raynaud's phenomenon. The other died at age 29 years, 4 years after the apparently valid diagnosis of Raynaud's disease was made, and 14 years after the onset of Raynaud's phenomenon. The final diagnoses in these 2 cases are in doubt, since necropsy data are not available. Raynaud's phenomenon may have been incidental and not secondary to the fatal illnesses.

One woman died of polyarteritis nodosa when 39 years old, 1 year after an apparently valid diagnosis of Raynaud's disease was made and 8 years after the onset of Raynaud's phenomenon.

In the last of the 13 patients thought to have Raynaud's disease, a bizarre type of muscular atrophy and primary biliary cirrhosis (both confirmed at the clinic) developed 8 years after the diagnosis of Raynaud's disease was made and 13 years after the onset of Raynaud's phenomenon. Again, the relationship of Raynaud's phenomenon to the disease of muscle and liver is problematic, but for the purposes of

TABLE 1.—*Revised or Verified Diagnoses According to Criteria of Allen and Brown for 629 Patients Suspected of Having Raynaud's Disease*

Original diagnosis	Total cases	Revised or verified diagnosis	
		Raynaud's disease	Questionable Raynaud's disease*
Raynaud's disease...	514	353	161
Questionable Raynaud's disease...	115	24	91
Total.....	629	377	252

* Reasons for doubtful diagnosis listed in table 2.

TABLE 2.—*Final Diagnoses for 629 Patients Suspected of Having Raynaud's Disease*

Revised or verified diagnosis (by Allen-Brown criteria)	Cases	Final diagnosis (from follow-up data)	Cases
Raynaud's disease	377	Raynaud's disease	267
		Disease developed to which Raynaud's phenomenon may have been secondary	13
		No follow-up but presumed to be Raynaud's disease	97
Questionable Raynaud's disease	252	Raynaud's disease	110
Reason			
Duration not stated	56	Dead (see table 3)	37
Duration inadequate	138	Raynaud's phenomenon disappeared	29
Pulsations absent or not recorded	17	Rheumatoid arthritis	15
Unilateral	14	Acrosclerosis	12
Possibly secondary to other disease	27	Dermatomyositis	1
		Raynaud's phenomenon still unilateral	4
		No follow-up	44

TABLE 3.—*Causes of Death in 37 Cases of Questionable Raynaud's Disease*

Cause	Deaths
Unknown	19
Disseminated lupus erythematosus	6
Proved 2	
Suspected 4	
Carcinoma	3
Stomach 1	
Breast 1	
Uterus 1	
Miscellaneous*	9

* Includes 1 case each of: muscular atrophy, cerebral arteriosclerosis, malignant hypertension, pneumonia, hemorrhagic diathesis, possible selenium poisoning, acute nephritis, possible Addison's disease, and possible scleroderma.

TABLE 4.—*Ages at Death in 37 Cases of Questionable Raynaud's Disease*

Age (years)	Deaths
10–19	1
20–29	8
30–39	4
40–49	7
50–59	5
60–69	1
70 or more	7
Unknown	4
Youngest 14 yr.	
Oldest 96 yr.	
Average 47 yr.	

this paper Raynaud's phenomenon has been presumed to be a secondary manifestation.

Validity of the Diagnosis of Questionable Raynaud's Disease Based on Allen-Brown Criteria. The revised diagnosis was questionable Raynaud's disease for 252 patients. Follow-up data could not be obtained on 44 of these patients. The diagnosis of Raynaud's disease was verified by the follow-up information for 110 (53 per cent) of the 208 female patients on whom such data were available. The results of follow-up study for the remainder are shown in table 2.

Follow-up information revealed the rather startling fact that 37 patients for whom a diagnosis of questionable Raynaud's disease was made (17.8 per cent of those with follow-up data available) had died; more than half before the age of 50. The causes of death are listed in table 3, and the ages at time of death are listed in table 4. Nineteen of the 37 deaths occurred within 5 years of the time that the patients were first seen at the clinic. Twenty-eight of the patients who subsequently died had noted Raynaud's phenomenon for less than 2 years when they were seen at the clinic.

ANALYSIS OF DATA FROM 474 PATIENTS

The next part of this paper is devoted to the analysis of data derived from the records of the 474 women and girls for whom the final diagnosis was Raynaud's disease (table 2). The diagnosis was made according to the criteria of Allen and Brown either from the records of the initial examination or from follow-up data or examination.

Age at Onset. The age at which Raynaud's phenomenon first appeared was known for 425 of the 474 female patients with Raynaud's disease (table 5). The earliest age of onset was 4 years, the latest was 68 years, and the average age was 31 years. Seventy-eight per cent of the patients were 39 years old or less at onset.

Location of Raynaud's Phenomenon. The fingers of 467 of the 474 patients were the site of color change when they were first seen at the clinic. In 4, only the toes were involved, and in 3 the sites of involvement were not clearly stated. In 259 patients the fingers only were involved, and in 202 patients both the fingers and toes were involved. Involvement of the nose, ears, face, chest or lips also occurred in 6 cases. Initially, Raynaud's phenomenon was unilateral, involving the fingers of 1 hand in 10 cases. The longest duration of unilateral Raynaud's phenomenon at the time of the initial visit to the clinic was 5 years, and this was reported by only 1 patient; the average duration was 2½ years. In all 10 of these patients Raynaud's phenomenon eventually occurred bilaterally.

Precipitating Factors. Exposure to cold was the only stimulus for precipitating Raynaud's phenomenon in 365 patients. Emotional reactions were the only precipitating factors in 4 patients, and 85 stated that both exposure to cold and emotional reactions were responsible. In addition to exposure to cold, tea and coffee

were implicated by 1 patient and pressure by another. Eight patients could cite no precipitating factors and 10 records were not clear on this point. Strict adherence to the first criterion of Allen and Brown would have led to discarding these 18 cases. However, the absence of any disease to which Raynaud's phenomenon might have been secondary made it difficult to classify these cases as anything but Raynaud's disease.

Duration of Symptoms. Raynaud's phenomenon had been present for as brief a period as 1 month and for as long as 40 years when these patients were first seen at the clinic for this complaint (table 5). The average duration was 7 years. The records of 49 patients were not clear as to the exact duration, but such phrases as "many years," "all her life" and "since girlhood," indicated long duration for most of these. In all cases in which the duration of symptoms was in doubt or less than 2 years at the time of the initial examination, when the follow-up data were obtained Raynaud's phenomenon had been present for at least 2 years.

Phases of Color Change. Although the classical description of Raynaud's phenomenon includes a 3-phase color change from pallor to cyanosis to rubor, this was not always observed. Only 133 of the 474 records contained detailed descriptions of the color changes. Of these 133, 87 (65 per cent) described the typical 3-phase color change; 29 (22 per cent) described only a 2-phase color change and 17 (13 per cent) described only 1 phase of the color change (usually pallor, occasionally cyanosis).

Family History. Twenty of the 474 patients knew of 1 or more relatives who had Raynaud's phenomenon. These consisted of a sister in 6 cases, a mother in 4 cases, a mother and father in 1 case, a sister and daughter in 1, a father in 1, a brother in 1, and a father and sister in 1. In 5 cases the relationship of the affected kin was not clearly stated.

Associated Diagnoses. A variety of functional complaints were commonly associated with Raynaud's disease. One hundred seventy-nine (38 per cent) of the 474 patients in this group had one or more of the following included in the final diagnosis: Chronic nervous exhaustion in 74 cases, various types of psychoneurosis in 44, chronic constipation in 31, anxiety state in 21, irritable bowel in 11, tension state in 9, obesity in 8, dysmenorrhea in 8, pain in the chest wall in 6, and functional gastrointestinal disorder in 6. Many other similar diagnoses were made in 5 cases or less. Many other patients had similar complaints, that were not included, however, in the final diagnoses.

TABLE 5.—*Raynaud's Disease among 474 Patients*

Age at onset		Duration of symptoms at first visit to clinic for this complaint	
Age (years)	Patients	Duration (years)	Patients
0–9	8	Less than 2	62
10–19	74	2–5	190
20–29	123	6–10	89
30–39	127	11–15	37
40–49	59	16–20	25
50–59	26	21–40	22
60–69	8		
Indefinite or not stated	49	Indefinite or not stated	49

Migraine headache was diagnosed in 65 (14 per cent) of the 474 patients. Hypertension (blood pressure greater than 150 mm. Hg systolic and 90 mm. Hg diastolic) was present in 43 (9 per cent) of the 474. These figures include 10 cases in which hypertension and migraine headache coexisted.

Incidence of Complications at First Examination. At the time of the initial examination at the clinic for Raynaud's phenomenon, 63 (13 per cent) of the 474 patients had or gave a history of having had trophic changes (ulceration, chronic paronychia, necrosis, scarring, fissuring) of one or more digits. The toes of only 4 were involved in the trophic changes. The duration of Raynaud's phenomenon for these 63 patients varied from 1½ to 35 years, and the average duration was 8½ years.

At the time of the initial examination at the clinic for Raynaud's phenomenon, 57 (12 per cent) had evidence of sclerodactylia involving the fingers (in only 1 patient was sclerodactylia noted in the toes also). The duration of Raynaud's phenomenon for these 57 patients varied from 6 months to 35 years and the average duration was 8 years.

Twenty-three patients had both sclerodactylia and trophic changes of the digits when first

TABLE 6.—*Change in Raynaud's Phenomenon at Follow-up in 307 Patients with Raynaud's Disease*

Change reported	Patients	Per cent
No change	116	38
Improved	109	36
Worse	50	16
Disappeared	32	10
Total	307	100

seen at the clinic, and are included in both groups.

Calcinosis of the fingers was noted in only 1 patient at the time of the initial examination at the clinic. Amputations of terminal phalanges had been performed for complications of Raynaud's disease on 2 women (0.4 per cent) of the 474 before they came to the clinic the first time. One woman lost the terminal phalanx of 1 finger while the other lost terminal phalanges of 2 toes. These amputations were performed for nonhealing, painful, infected ulcers of the tips of the digits. True gangrene had not developed. Although both these women had Raynaud's disease by the criteria outlined, the woman who lost the terminal phalanges of 2 toes also had a more persistent mottled cyanosis of her lower extremities in addition to episodic Raynaud's phenomenon. She probably had livedo reticularis in addition to Raynaud's disease.

Amputation of an entire digit was performed on 1 additional patient at the time of her first admission to the clinic. The patient, a woman 68 years old, had had Raynaud's disease for 35 years at the time of amputation. The pathologic specimen revealed an atherosclerotic process obliterating the digital arteries. For this reason the amputation was attributed to occlusive arterial disease and not to coexisting Raynaud's disease.

COURSE AND PROGNOSIS

Of the 474 female patients with Raynaud's disease, 397 were treated conservatively and 77 were subjected or had previously been subjected to surgical sympathetic denervation of 1 or more extremities. These latter patients will be considered in a separate communication.

Follow-up information was obtained by questionnaire or by re-examination at the clinic for 307 of the 397 treated medically. Medical treatment of this group consisted largely of reassurance and protection of the extremities from cold and trauma with or without whatever medicinal agents were in vogue at the particular time the patients were seen. The age at onset, location, duration, phases of color change, family history of Raynaud's phenomenon, and incidence of associated diagnoses were all similar to those for the entire group. The incidences of sclerodactylia (9 per cent) and of trophic changes (5 per cent) were less than those of the entire group, since many of the patients with these complications were treated surgically.

Duration of Follow-up. The shortest span of follow-up from the first examination at the clinic for Raynaud's phenomenon was 1 year, the longest was 32 years, and the mean duration was 12 years. The duration of symptoms from the onset of Raynaud's phenomenon (when known) to the end of the follow-up period varied from 3 to 46 years, and the mean duration of symptoms was 17 years for this group of 307 patients.

Course of Raynaud's Phenomenon. The data in table 6 were derived from the patients' estimations of the severity and frequency of symptoms at the time of follow-up. Spread of Raynaud's phenomenon to parts originally uninvolved is not taken into consideration in table 6, since some patients reported that the symptoms had improved or remained unchanged but that other extremities had become involved. Spread to the toes did not necessarily represent an increase in severity. Our data also fail to portray any temporary variations in severity that may have occurred. For instance, the symptoms may have become worse after the first examination at the clinic and then gradually improved, or the reverse may have occurred. Therefore, improvement or worsening does not necessarily imply that the entire course has been in one direction or the other.

All patients who reported that Raynaud's phenomenon disappeared had had symptoms for at least 2 years before it disappeared, and an adequate diagnosis of Raynaud's disease had been made at the clinic.

Accurate data on smoking habits were available for 278 patients. Of 203 who did not smoke,

90 (44 per cent) observed improvement or disappearance of Raynaud's phenomenon. Of 34 who smoked an average of 10 or more cigarets a day, 16 (47 per cent) observed improvement or disappearance of Raynaud's phenomenon.

Twenty-five (57 per cent) of the 44 patients who moved to a warmer climate reported improvement or disappearance of Raynaud's phenomenon.

Forty patients who had Raynaud's phenomenon in the fingers only when first examined reported on follow-up that it also had appeared in the toes.

Course of Existing Complications. Fifteen (5 per cent) of the 307 patients had, or gave a history of trophic changes in one or more digits when they were first examined at the clinic. Six of these 15 patients also had sclerodactylia. Thirteen had no further difficulty with trophic lesions, but one later had sclerodactylia. Two continued to have trophic lesions.

Twenty-seven (9 per cent) of the 307 patients had sclerodactylia when they were first examined at the clinic. This includes the 6 who also had trophic lesions. Sclerodactylia disappeared in 19 (70 per cent), remained unchanged in 7 (in 1 of whom trophic lesions developed), and adequate follow-up was not available in 1.

Follow-up data were obtained for both women who had had amputations of terminal phalanges for complications of Raynaud's disease before coming to the clinic for the first time. One who lost the terminal phalanx of a finger was followed for 7 years after cervicothoracic ganglionectomy, and the other who lost terminal phalanges of 2 toes was followed for 15 years of conservative treatment. Neither had any further complications of Raynaud's disease, and both reported that Raynaud's phenomenon had improved.

Incidence of New Complications. Two hundred seventy-one patients did not have sclerodactylia or trophic lesions of the fingers when they were first examined at the clinic, and 243 (90 per cent) of them remained free of these complications for the duration of the follow-up period. In 6 patients (2 per cent), follow-up information was inadequate. Nine patients (3.3 per cent) of those not having complications originally had sclerodactylia of the fingers during the follow-up period, 9 (3.3 per cent) first had trophic lesions of the fingers (and toes, 1 patient) in the follow-up period, and 4 (1.4 per cent) had both trophic lesions and sclerodactylia. Calcinosis developed in the fingers of 4 (1.3 per cent) of 307 patients.

No amputations were performed for complications of Raynaud's disease during the period of follow-up among the 307 conservatively treated patients. Arteriosclerosis obliterans of the lower extremities, however, developed in a woman aged 65 years, 29 years after a valid diagnosis of Raynaud's disease had been made at the clinic. Pulsations in the pedal arteries were not palpable when gangrene of the left second toe necessitated amputation of that digit. For this reason, Raynaud's disease was not considered responsible for the amputation.

Correlation was good between the severity of Raynaud's phenomenon and the development of complications during the follow-up period. Among 141 patients who reported that Raynaud's phenomenon improved or disappeared, only 4 (3 per cent) reported that sclerodactylia or trophic changes had developed. Conversely, in 9 (18 per cent) of 50 patients who reported worsening of Raynaud's phenomenon, sclerodactylia or trophic lesions or both developed during the period of follow-up. Most of the patients whose pre-existing sclerodactylia or trophic lesions improved or disappeared also reported concomitant improvement or disappearance of Raynaud's phenomenon.

Causes of Death. Twelve (4 per cent) of the 307 traced patients treated conservatively died during the period of follow-up (table 7). The ages at time of death varied from 39 to 86 years; the average age was 59 years. None of the deaths could be attributed in any way to Raynaud's disease. The course and progress of Raynaud's disease had no influence on death rate as the 12 deaths were proportionately distributed among the 4 groups shown in table 6.

Adequate follow-up data pertaining to Raynaud's disease were not available for 90 patients whose Raynaud's disease was treated conservatively. However, our attempts at follow-up disclosed that 22 of these patients were dead. Their ages at time of death varied from 35 to 77 years, and the average was 55 years.

TABLE 7.—*Causes and Time of 12 Deaths among 307 Patients with Raynaud's Disease*

Cause of death	Time of death		
	Age (years)	Years after onset of Raynaud's phenomenon	Years after first examination at clinic
Subacute bacterial endocarditis	39	>11*	11
Cirrhosis of liver and mesenteric thrombosis	42	27	1
Cerebral vascular accident	45	14	10
Carcinoma of stomach with hepatic metastasis	48	4	3
Accident	49	31	8
Carcinoma of liver	50	8	4
Indeterminate lesion of nervous system with paralysis	57	13	3
Unknown	57	14	10
Cerebral vascular accident	75	>8*	8
Unknown	76	31	29
Cerebral vascular accident	81	24	22
Gangrene of feet and legs†	86	30	26

* Date of onset of Raynaud's phenomenon not clearly stated.

† Presumably owing to arteriosclerosis obliterans. Raynaud's phenomenon had disappeared before death.

The causes of death were known for 10 and included cirrhosis of the liver in 2, hypertensive heart disease in 2, postoperative deaths in 2, and carcinoma of the rectum, Bright's disease, "circulatory collapse," and accidental death in 1 each.

DISCUSSION

It is interesting that 8 patients in whom the final diagnosis was Raynaud's disease could not implicate cold or emotional reactions as precipitating factors for Raynaud's phenomenon. Follow-up information convinced us that all 8 had Raynaud's disease.

It is also interesting that a few patients who were subsequently proved to have Raynaud's disease, first noted unilateral Raynaud's phenomenon for several years before it became bilateral. Hines and Christensen[1] reported the occurrence of unilateral Raynaud's phenomenon in several men for whom the diagnosis of Raynaud's disease seemed adequate otherwise.

Raynaud's phenomenon may be a manifestation of serious and disabling diseases. Follow-up studies revealed that of 208 female patients who had Raynaud's phenomenon, but for whom the diagnosis of Raynaud's disease could not be confirmed by the criteria of Allen and Brown at the time of revision or on follow-up, 37 (17.8 per cent) had died. The causes of death were not learned for more than half of these patients, but the fact that 13 of the 37 deaths occurred before the patients were 40 years of age is certainly indicative that in many of the cases Raynaud's phenomenon was a secondary manifestation of serious underlying disease.

The most common and least serious cause of Raynaud's phenomenon is Raynaud's disease. When this diagnosis can be verified, the physician has every right to reassure the afflicted patient. Raynaud's disease was not implicated in any of the deaths that occurred among this group of patients, and indeed, if there is a mortality rate for Raynaud's disease, it is negligible. In this series, the average age at death for those patients who succumbed during the period of follow-up was less than 60 years, but this figure is not significant, since 96 per cent of the patients were still living when the study was completed. It is our present impression that Raynaud's disease is not incompatible with a normal span of life.

Uncomplicated Raynaud's disease may be responsible for inconvenience in that the extremities must be protected from cold and trauma, but it is usually not disabling. Whereas 46 per cent reported that their symptoms improved or disappeared, only 16 per cent of conservatively treated patients reported increase in the severity or frequency of Raynaud's phenomenon during the follow-up period. Sympathectomy might have been helpful for some of the latter, but for various reasons was not performed. Blain, Coller, and Carver[6] have reported that 31 per cent of their patients with Raynaud's disease noted moderate or severe progression of symptoms. The discrepancy is easily explained by the fact that Blain and his colleagues were reporting on patients treated surgically as well as nonsurgically

whereas we have confined the follow-up data in this report to patients not treated surgically. It is only natural that patients with the more severe and progressive disease should be selected for surgical treatment. It must be emphasized, however, that many of our conservatively treated patients were advised to have sympathectomy but refused it.

Morbidity, in the form of trophic lesions of the digits or sclerodactylia or both, had occurred at or prior to the first examination at the clinic for 20 per cent of our 474 patients with Raynaud's disease. For many, the symptoms were mild and not incapacitating; amputations of terminal phalanges for Raynaud's disease had been necessary on only 2 patients (0.4 per cent) before their first examinations at the clinic. These figures are representative, since they include all patients regardless of subsequent treatment. For the 307 patients who were treated conservatively, follow-up data revealed that only 8 per cent of those initially free of these complications subsequently had sclerodactylia or trophic lesions or both, which did not lead to amputation in a single instance. Among this same group, trophic lesions or sclerodactylia or both disappeared during the period of follow-up in most patients. This may indicate that sclerodactylia is a reversible process, but we are hesitant to state this definitely because most of this information was obtained from follow-up questionnaires without benefit of reexaminations. Some patients are not aware of minimal sclerodactylia and may have given an erroneously negative reply to the question, "Is there any thickening of the skin on your fingers?" If present, however, sclerodactylia was certainly not incapacitating.

Raynaud's disease was not responsible for extensive gangrene or major amputations in any patient. By Raynaud's original definition[2] and by the subsequent criteria of Allen and Brown[4, 5] Raynaud's disease cannot cause extensive gangrene. In this study we did not discard any case solely on the basis of this one criterion. When the other criteria for diagnosis were satisfied, Raynaud's disease did not produce extensive gangrene. When massive gangrene does occur, other causes for Raynaud's phenomenon can usually be found, as demonstrated by Allen and Brown[4] for some of Raynaud's cases and others in the literature.

In all major respects, the results of this study are in agreement with those of Hines and Christensen[1] in their study of Raynaud's disease in men. Emotional reactions play a greater role in precipitating the vasospastic episodes in the females and the classical 3-phase color changes were observed more frequently among the females. Neither study produced any evidence that use of tobacco influenced the course of the disease. In approximately 10 per cent of both groups, Raynaud's phenomenon disappeared during the period of follow-up. No cause for Raynaud's phenomenon was evident; it, therefore, seems that these cases represent true Raynaud's disease in which spontaneous "cure" or remission has occurred.

It is interesting that the symptoms of 6 women improved or disappeared during or following the menopause and in 3 improved during pregnancy. None stated that menopause or pregnancy aggravated their symptoms. Migraine headache or hypertension or both had no influence on the subsequent course of Raynaud's disease in our patients.

Like Blain, Coller, and Carver[6] we are impressed that Raynaud's disease is less likely to be severe and progressive if the onset occurs early or late in life. None of our patients who first noted symptoms before age 10 years or after age 55 years had serious or disabling complications.

Blain and his group stated that the disease tended to be more severe when emotional factors precipitated the vasospastic episodes. This was not true in our group of conservatively treated patients.

Although our data are not suitable for determining accurately the interval between the onset of Raynaud's phenomenon and the occurrence of complications when present, it is certain that the incidence of sclerodactylia and trophic changes does not increase appreciably after the first decade of the disease and we are inclined to agree with the findings of Blain and associates[6] that in the majority of cases progress to the severe state will occur within 1 to 7 years of the onset of the disease.

Our findings again confirm the relative

benignity of Raynaud's disease as originally defined by Raynaud[2, 7] and as emphasized by other follow-up studies.[1, 6] Nevertheless, Raynaud's disease continues to have sinister connotations for many patients and physicians.

Summary

From 1920 through 1945, the diagnosis of Raynaud's disease was made or suspected for 756 women and girls at the Mayo Clinic. When the diagnoses were revised according to the criteria of Allen and Brown, the original diagnosis of Raynaud's disease was considered incorrect for 127 patients and was considered questionable for 252. Follow-up information was available from 208 of the 252 patients with a questionable diagnosis. This revealed that 52.9 per cent did have Raynaud's disease. In 13.5 per cent, diseases with which Raynaud's phenomenon is commonly associated (rheumatoid arthritis, acrosclerosis, and dermatomyositis) developed. The Raynaud phenomenon subsequently disappeared in 13.9 per cent and remained unilateral in 1.9 per cent. The remaining 17.8 per cent were dead. Six patients were known or were presumed to have died of disseminated lupus erythematosus with which Raynaud's phenomenon is commonly associated. Although the causes of death were not known for 19 patients, the young age at which many of them died suggests that their Raynaud's phenomenon may have been secondary to a serious disease.

When Raynaud's phenomenon occurs, the prognosis is uncertain until a diagnosis of Raynaud's disease can be validated by the criteria of Allen and Brown. This study has shown that the diagnosis of Raynaud's disease by these criteria will be accurate in at least 95 per cent of the cases.

Review of the records of 474 women and girls who had Raynaud's disease and follow-up information obtained from 307 who were treated conservatively confirms the benignancy of this disease. There were no deaths attributed to it, and very little disability. Amputations of terminal phalanges for complications of Raynaud's disease were necessary for 0.4 per cent of the patients before coming to the clinic and for none during the follow-up period. Raynaud's phenomenon became less troublesome or disappeared in 46 per cent. Trophic lesions of the fingers and sclerodactylia improved or disappeared in the majority of women who had these complications. No major amputations were necessary and gangrene did not occur in any case.

Raynaud's phenomenon can be a manifestation of many conditions and diseases of which Raynaud's disease is the most common and least serious.

Acknowledgment

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Summario in Interlingua

Ab 1920 usque al fin de 1945, le diagnose de morbo de Raynaud esseva facite o suspicite al Clinica Mayo in 756 feminas e pueras. Le revision del diagnoses secundo le criterios de Allen e Brown resultava in le conclusion que le constatation original de morbo de Raynaud esseva incorrecte in 127 patientes e questionabile in 252. Informationes ulterior esseva disponibile pro 208 del 252 patientes con diagnoses questionabile. Iste informationes ulterior revelava que 52,9 pro cento del patientes in iste gruppo habeva de facto morbo de Raynaud. In 13,5 pro cento, morbos se disveloppava con que le phenomeno de Raynaud es communmente associate (i.e. arthritis rheumatoide, acrosclerosis, e dermatomyositis). Le phenomeno de Raynaud dispareva subsequentemente in 13,9 pro cento del casos e remaneva unilateral in 1,9 pro cento. Le remanente 17,8 pro cento del patientes esseva morte. Sex patientes habeva morite certe– o presumitemente ab disseminate lupus erythematose con que le phenomeno de Raynaud es communmente associate. Ben que le causa de morte non esseva cognoscite in 19 casos, le juvene etate a que multes de iste patientes moriva suggere que lor phenomeno de Raynaud esseva possibilemente secundari a un serie morbo.

Quando le phenomeno de Raynaud occurre, le prognose es incerte usque le diagnose de

morbo de Raynaud pote esser corroborate secundo le criterios de Allen e Brown. Le presente studio ha monstrate que le diagnose de morbo de Raynaud secundo le criterios de Allen e Brown es accurate in al minus 95 pro cento del casos.

Le examine del protocollos de 474 feminas e pueras con morbo de Raynaud, insimul con informationes ulterior pro 307 de illas in qui le tractamento usate esseva de character conservatori, confirma le benignitate de iste morbo. Nulle morte esseva attribuite a illo e pauchissime invaliditate. Amputation de phalanges terminal a causa de complicationes de morbo de Raynaud esseva necessari in 0,4 pro cento del patientes ante lor arrivata a iste Clinica e in nulle durante le periodo ulterior. Le phenomeno de Raynaud deveniva minus incommodante o dispareva in 46 pro cento del casos. Lesiones trophic del digitos e sclerodactylia se meliorava o dispareva in le majoritate del feminas qui habeva iste complicationes. Nulle amputationes major esseva necessari, e nulle gangrena occurreva in ulle del casos. Le phenomeno de Raynaud pote esser un manifestation de numerose conditiones e morbos. Inter illos, morbo de Raynaud es le plus commun e le minus serie.

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The danger of sudden abolition of the carotid sinus reflex does not seem to be generally appreciated. Bucy pointed out in 1936 that section of 1 glossopharyngeal nerve could cause elevation of blood pressure. In 4 of 5 patients the blood pressure rose promptly after sectioning and remained elevated for 5 to 12 days. In the 49-year-old man described by the author, blood pressure rose from 120/80 to 240/140 mm. Hg while the patient was still on the surgical table. He never recovered consciousness and died 24 hours after operation. There was increased cerebrospinal fluid pressure and 40 red cells per $mm.^3$ in the spinal fluid. Multiple cerebral hemorrhages were discovered at autopsy. The author suggests that irradiation might have advantage as treatment by reducing hyperactivity slowly. He also suggests vigilant control of blood pressure with hypotensive agents at the time of surgery.

McKUSICK

Nonparoxysmal A-V Nodal Tachycardia

By ALFRED PICK, M.D., AND PEDRO DOMINGUEZ, M.D.

Acceleration of impulse formation in the ordinarily subsidiary A-V nodal pacemaker is manifested in clinical electrocardiograms in a paroxysmal and a nonparoxysmal variety. The former occurs as a rule in normal hearts, the latter in pathologic conditions, frequently, but not invariably also causing A-V block. The electrocardiographic and clinical aspects of nonparoxysmal nodal tachycardia were studied in 30 cases and the relative importance of the disturbance was evaluated in 3 conditions in which it is found most frequently, namely, digitalis effect, acute rheumatic fever, and recent posterior wall infarction.

MANIFESTATIONS of the pacemaker function of the A-V node are, according to current concepts, classified into 2 types[1]:

1. A "passive" form in which the A-V node escapes[2] the control of the primary pacemaker because the latter releases impulses at a slower rate than the A-V node, or because primary (sinus) impulses, discharged at a normal rate, are prevented by a block from reaching the secondary pacemaker and suppressing its activity.

2. An "active" form in which the A-V node gains control of ventricular or atrial activation by virtue of a sudden and marked enhancement of impulse formation resulting in single or a run of premature beats—rapid rhythms of the latter type being termed paroxysmal A-V nodal tachycardias. In interpreting clinical electrocardiograms[3] the range of rates of "passive" nodal rhythms was found to vary between about 35 and 50 and that of paroxysmal nodal tachycardias between about 150 and 220.

The present report deals with a type of enhanced A-V nodal activity that does not conform with the above criteria in 2 respects: (1) the rate of the nodal discharge is only moderately accelerated, from about 70 to 130 and (2) the ectopic rhythm lacks the sudden onset and abrupt termination characteristic of the paroxysmal forms of nodal tachycardias. The existence of this type of ectopic impulse formation has been recognized in the past but variously named. Some of these designations, for example A-V dissociation,[4, 5] interference-dissociation,[6, 7] dissociation with interference,[8, 9] and isorhythmic dissociation,[10] merely define secondary effects upon the cardiac mechanism rather than the primary disturbance; others, such as ventricular escape,[11, 12] atrioventricular (nodal) rhythm,[13, 14] and complete heart block,[15-18] are in our opinion entirely inadequate. We propose the unifying term *nonparoxysmal A-V nodal tachycardia*, with an added short statement defining its consequences.

It appeared to us that nonparoxysmal nodal tachycardia with its several electrocardiographic facets may represent an entity whose significance has as yet not been fully appreciated in clinical cardiology. A number of electrocardiograms of this category were therefore submitted to detailed analysis and correlated with clinical data in order to assess the factors determining the variety of electrocardiographic features of this type of nodal activity and to evaluate its relative importance in the 3 specific conditions in which it was found most frequently.

MATERIAL AND METHODS

From the files of the Heart Station of the Michael Reese Hospital 30 nonconsecutive cases were selected that revealed in the electrocardiogram, at one time or another, persistent or intermittent rhythms of A-V nodal origin at rates ranging from 70 to 130. This selection was made regardless of whether the ectopic rhythm had led to retrograde activation of the atria or to A-V dissociation. However, cases were excluded in which only a short and transitory period of nodal acceleration had been elicited by anesthesia or surgery, cardiac catheterization, or the exhibition of atropine, procaine amide (Pronestyl), or isoproterenol (Isuprel). Pertinent clinical and electrocardiographic data of the 30 cases are assembled in table 1 according to the

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TABLE 1.—*Clinical and Electrocardiographic Findings in Thirty Cases with Nonparoxysmal A-V Nodal Tachycardia*

Case no.	Age (yrs.)	Clinical diagnosis	Cause of ectopic rhythm	Ectopic rate (beats/min.)	Basic rhythm	A-V block present	Resulting disturbance
1	56	HHD, CHF	Digitalis	75	AF	Yes	Complete A-V dissoc.
2	51	H & AHD old ant. infarct	Digitalis	78	SR	Yes	Incomplete A-V dissoc.
3	45	RHD, CHF	Digitalis	75	AF	Yes	Intermittent A-V dissoc.
4	69	Pneumonia, CHF	Digitalis	73	SR	Yes	Incomplete A-V dissoc.
5	67	AHD, CHF	Digitalis	80	SR (with S-A block)	Yes	Intermittent A-V dissoc.
6	57	AHD	Digitalis	94	SR	Yes	Complete A-V dissoc.
7	69	Emphysema, AHD	Digitalis	83	SR	?	Complete A-V dissoc.
8	44	HHD	Digitalis	107	SR	?	Incomplete A-V dissoc.
9	61	H & AHD, CHF	Digitalis	110	AF	Yes	Complete A-V dissoc.
10	50	HHD, uremia	Digitalis	86	SR	?	Incomplete A-V dissoc.
11	70	AHD	Digitalis	79	ST	Yes	Incomplete A-V dissoc.
12	83	AHD, CHF	Digitalis	94	AF	Yes	Complete A-V dissoc.
13	43	RHD, CHF	Digitalis	111	SA	Yes	Complete A-V dissoc.
14 (fig. 2)	65	AHD, CHF	Digitalis	68 → 75	AF	Yes	Complete A-V dissoc.
15	75	AHD, CHF	Digitalis	100	ST	?	Incomplete A-V dissoc.
16	84	HHD, CHF	Digitalis	75	SA	No	Retrograde conduction → incomplete A-V dissoc.
17	9	ARF	Carditis	130	ST	No	Incomplete A-V dissoc.
18	15	RHD—reactivated	Carditis	107–130	ST	No	Incomplete A-V dissoc.
19 (fig. 4)	7	ARF	Carditis	136	ST	No → Yes	Incomplete → complete A-V dissoc.
20	3	ARF	Carditis	85	SA	No	Intermittent A-V dissoc.
21	7	ARF	Carditis	88	SA	No	Intermittent A-V dissoc.
22 (fig. 5)	12	ARF	Carditis	120 → 60	ST → SA	No	Incomplete → intermittent A-V dissoc.
23	23	ARF	Carditis	100	SA	No	Incomplete A-V dissoc.
24	62	MI	Recent post. infarct	75	SA	No	Intermittent A-V dissoc.
25	75	MI	Recent post. infarct	71	SA	No	Intermittent A-V dissoc.
26 (fig. 3)	40	MI M	Recent post. infarct	75	SA	No	Intermittent A-V dissoc.

TABLE 1.—*Continued*

Case no.	Age (yrs.)	Clinical diagnosis	Cause of ectopic rhythm	Ectopic rate (beats/min.)	Basic rhythm	A-V block present	Resulting disturbance
27	55	MI	Recent post. infarct	70	SR	Yes	Incomplete A-V dissoc.
28	67	Acute cholecystitis	?	107	?	No	Retrograde conduction
29	25	Anxiety	?	93	SR	No	Retrograde conduction
30 (fig. 1)	32	Trilogy of Fallot	?	96–107	SA	No	Retrograde conduction

HHD, Hypertensive heart disease.
AHD, Arteriosclerotic heart disease.
RHD, Rheumatic heart disease.
CHF, Congestive heart failure.
ARF, Acute rheumatic fever.
MI, Myocardial infarction.
SR, Sinus rhythm.
ST, Sinus tachycardia.
SA, Sinus arrhythmia.
AF, Atrial fibrillation.

established cause of the nodal tachycardia. Thus, the first and largest group consists of 16 cases in which a nonparoxysmal nodal tachycardia was encountered in the course of protracted or acute digitalization. The second group comprises 7 instances during acute rheumatic fever. In a third group of 4 cases the disturbance was found during early stages of posterior wall infarction. A final group of 3 consists of instances with 3 different and completely unrelated diagnoses and in which the cause of the protracted acceleration of the subsidiary pacemaker could not be established on clinical grounds.

In analyzing electrocardiographic and clinical data of these cases primary attention was paid to the following points: (a) the mode of onset, perpetuation, and termination of the nodal tachycardia, (b) the various secondary effects of the disturbance with regard to the pre-existent fundamental rhythm, (c) the presence or absence of a pre-existent, simultaneous, or subsequent disturbance of A-V conductivity, and (d) the correlation of serial electrocardiograms with all the clinical data. Representative examples of nonparoxysmal nodal tachycardia and of resulting simple or complex disorders of rhythm are illustrated in figures 1–5.

In figure 1 (case 30) a gradual acceleration, from 96 to 107, is seen in both the atrial and ventricular rates. Concomitantly, the P waves become at first smaller and then inverted, while the P-R interval shortens from 0.16 to 0.12 second. Toward the end of the tracing, the P waves gradually return to their original upright contour and P-R lengthens to 0.16 second, whereas the rate remains at 107. Thus, here, unlike paroxysmal nodal tachycardia, the A-V nodal pacemaker accelerates pari passu with speeding up of the sinus pacemaker. At first the 2 compete for the control of the atria with atrial fusion beats resulting; soon the nodal tachycardia exceeds the sinus tachycardia and nodal impulses dominate both the atria and ventricles; eventually the nodal pacemaker loses, and the sinus pacemaker gains speed. As a consequence, after another short period of competition, the sinus pacemaker once again controls both the atria and ventricles.

In figure 2 (case 14), on 12-1, adequate digitalization is evident from the ST-T configuration, the slow ventricular rate (averaging 55) during atrial fibrillation, and the occurrence of 2 nodal escapes (*E*); the latter are diagnosed on the basis of the equal R-R intervals (1.28 seconds, corresponding to a rate of 47)—the longest of the entire record.

On 12-4 and 12-5, the ST-T deformation is more marked and the ventricular rate is regular throughout. In the presence of atrial fibrillation this regularity indicates complete A-V dissociation. The nodal cycle is shorter than before, corresponding on 12-4 to a rate of 62, and 72 on the following day.

The record on 12-15 (10 days after digitalis was stopped) resembles that on 12-1, in that the ST-T abnormality is less marked and the ventricular action is irregular except for 2 nodal escapes (*E*). However, the average ventricular rate (75) as well as the nodal escape rate (65) are faster than originally.

The sequence of events in this series of records demonstrates the 2-fold action of digitalis upon A-V junctional tissues, depression of impulse transmission and enhancement of impulse formation. Here the 2 effects can be clearly separated. Impairment of conductivity preceded the acceleration of rhythmicity but, after withdrawal of the drug, the latter outlasted the former. The development of A-V dissociation coincided with the progressive speeding up of nodal impulse formation. Hence, it appears that the rapid sequence of nodal impulses preventing recovery of A-V junctional tissues was the actual factor responsible for the onset of the dissociation rather than a complete block of A-V conduction.

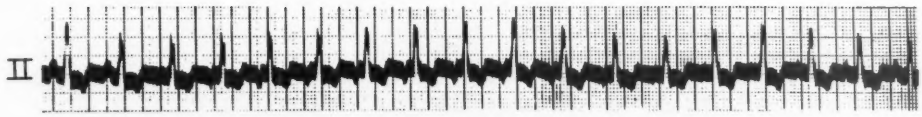

FIG. 1. The mode of onset and termination of a nonparoxysmal A-V nodal tachycardia, leading to retrograde activation of the atria (case 30).

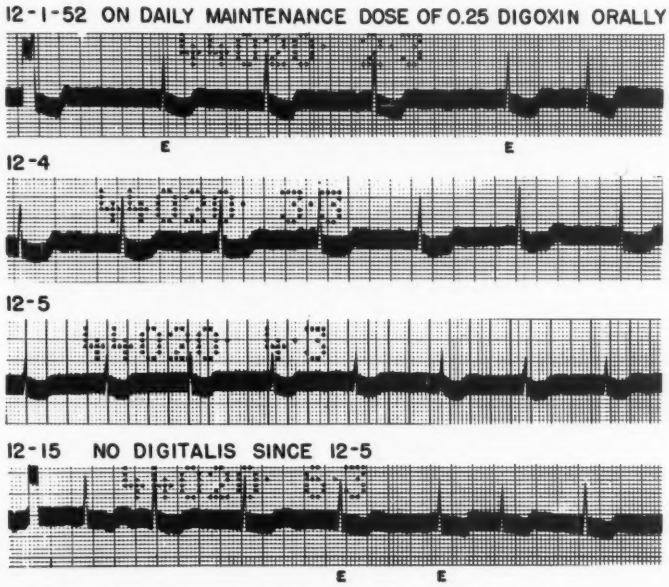

FIG. 2. Digitalis-induced nonparoxysmal A-V nodal tachycardia, as a cause of A-V dissociation in atrial fibrillation (case 14).

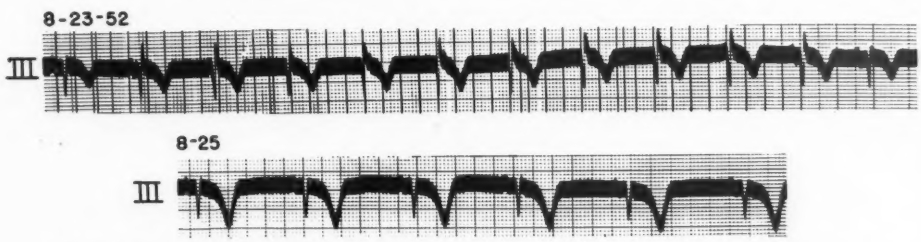

FIG. 3. Nonparoxysmal A-V nodal tachycardia in recent posterior wall infarction causing intermittent complete A-V dissociation (in the absence of A-V block) (case 26).

In figure 3 (case 26) the record of 8-23 shows complete A-V dissociation except for the first and last beats, which represent sinus beats conducted with a normal P-R of 0.14 second. During the A-V dissociation the ventricles are activated by an accelerated A-V nodal pacemaker (rate 75). Both sinus and ectopic beats reveal typical earmarks of posterior wall infarction but differ slightly in contour; this is attributed to the use of preferential A-V pathway by the nodal impulses.[21] The A-V dissociation commences when the rate of the irregular sinus pacemaker slows to 67; it continues while the sinus rate varies between 68 and 79 and disappears as soon as the sinus speeds up to 83.

The record of 8-25 shows a sinus bradycardia of 55, yet all beats are conducted with a normal P-R of 0.14 second. Evidently the nodal acceleration that caused the A-V dissociation on 8-23 must have subsided.

Involvement of A-V nodal function by recent

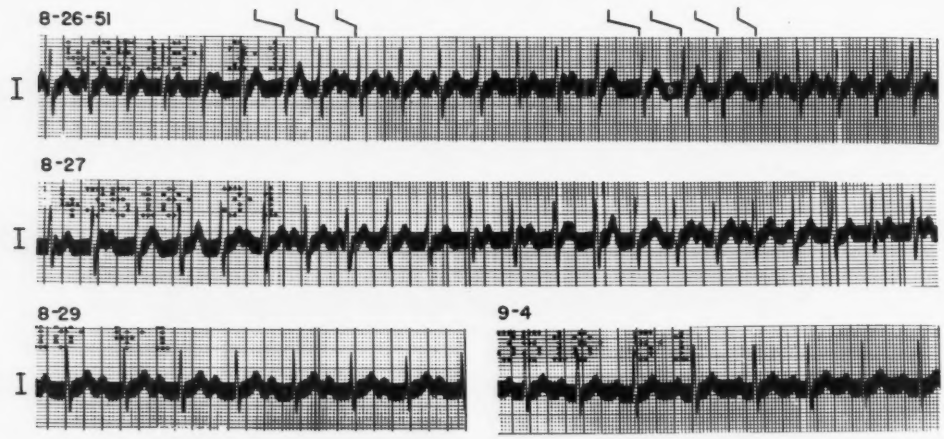

FIG. 4. Incomplete A-V dissociation due to nonparoxysmal A-V nodal tachycardia in acute rheumatic fever, changing to complete A-V dissociation with subsequent development of a first degree A-V block (case 19).

posterior wall infarction is a common event, usually manifested by a transient A-V block. In this instance only the property of impulse formation was affected while conductivity was entirely spared—as evident from the normal P-R interval of the conducted beats on both days. The failure of retrograde activation of the atria during the nodal tachycardia and the absence of ventricular captures during the ensuing A-V dissociation are the result of persistent physiologic A-V interference of sinus and nodal impulses operating at close rates.

In figure 4 (case 19), on 8-26, A-V dissociation is present because an accelerated A-V nodal pacemaker operates at a faster rate (136) than the simultaneously accelerated sinus pacemaker (125). The A-V dissociation is *incomplete*, since conductivity of the A-V node (in a forward direction) is unimpaired, as evident from the periodic recurrence of 3 or 4 successive ventricular captures (indicated by cutoff symbols). The last in this series of conducted sinus impulses has a P-R of 0.16 second; in the others, the P-R is prolonged to 0.34 or 0.36 second—a consequence of the normal state of relative refractoriness of A-V junctional tissues early in the nodal cycle. The R-R interval of these first captures is, contrary to the rule, prolonged instead of being shortened. This unusual finding compels the conclusion that: (a) part of the conduction delay of these captures took place in pathways below the site of the A-V nodal pacemaker which was prematurely discharged by the passing sinus impulse, and (b) the conduction time in this stretch of the A-V junction did not exceed the duration of the postponed nodal cycle.

On the following day (8-27), A-V dissociation is still present but the ventricular action is precisely regular—the A-V dissociation has become *complete*. Since on both days sinus and nodal rates are the same, and hence R-P relationships vary in a corresponding manner, the absence of ventricular captures on 8-27 must be ascribed to a new additional factor, namely prolongation of the refractory period of A-V junctional tissues impairing their conductivity.

That this was actually the case becomes evident in 2 subsequent tracings on 8-29 and 9-4, which reveal, following the disappearance of the nodal tachycardia, a slowly subsiding first degree A-V block (P-R 0.26 and 0.20 respectively).

This series of records, therefore, clearly shows the 2 manifestations of involvement of the A-V node by acute rheumatic fever and, in addition, that the 2 nodal functions, rhythmicity and conductivity, may be affected separately or together.

The diagram in figure 5*B* summarizes the clinical, laboratory, and electrocardiographic data of case 22 over a period of 16 days; the numbers in circles indicate the days on which the 3 electrocardiograms in figure 5*A* were obtained. The acute rheumatic process is evident from the temperature curve, the involvement of the joints, the development of an apical systolic murmur, the initial elevation of the leukocyte count and of the C-reactive protein (CRP), and the rising antistreptolysin titer (ASL). The broad shaded area represents the range of sinus arrhythmia, the black area the rate of a corresponding A-V nodal pacemaker, as noted in daily electrocardiograms. This correlation shows that at the height of the acute process the accelerated nodal rate permanently exceeded the range of the simultaneously accelerated sinus pacemaker with resulting persistent (incomplete) A-V dissociation (upper record in *A*). As rheumatic activity subsided, the rate of the 2 pacemakers dropped to similar average

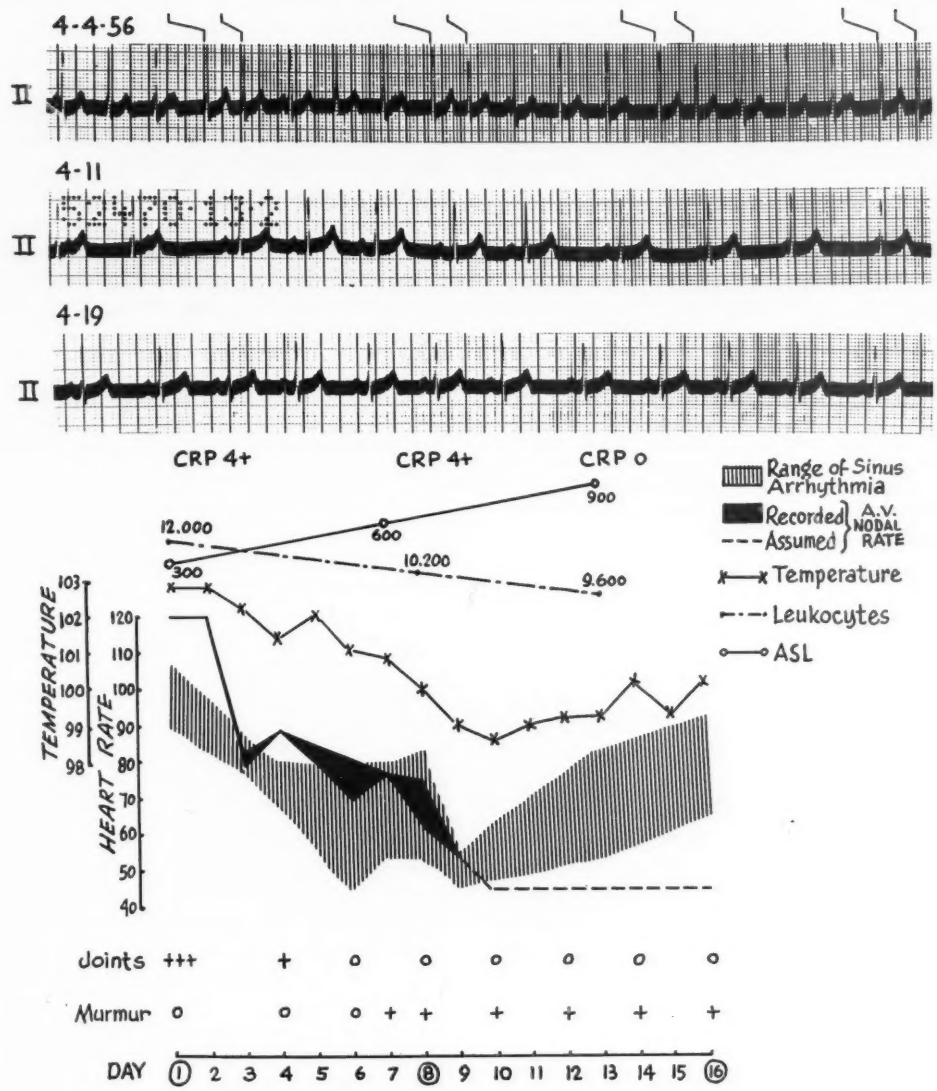

FIG. 5 *A*, *top* and *B*, *bottom*. The relation of a nonparoxysmal A-V nodal tachycardia (without A-V block) to other manifestations of acute rheumatic fever (case 22).

values; consequently A-V dissociation was observed only intermittently when the sinus rate, temporarily, became slower than that of the still accelerated and less irregular nodal pacemaker (middle record in *A*). Eventually, after a week, with further clinical improvement of the patient, signs of nodal activity disappeared from the electrocardiograms. Presumably the A-V node had returned to its normal function as a subsidiary pacemaker with an inherent rate of less than 60 (lowest record of *A*).

The following details should be noted in the 3 electrocardiograms:

1. On 4-4, the repetitive recurrence of 2 successive ventricular captures after every third nodal beat causes ventricular group beating. Only the second of each pair of captures reveals the characteristic R-R shortening; in the first, R-R is, against the rule, prolonged—and this for reasons outlined in the description of figure 4, where a corresponding finding is illustrated.

2. On 4-11, A-V dissociation is transiently replaced by 5 successively conducted sinus impulses, since at this time the sinus became faster than the nodal pacemaker. However, the first of these conducted sinus impulses (third P wave) occurs after a pause that exceeds by 0.14 second the longest nodal interval in the record. The failure of a nodal beat to terminate this pause is attributed to concealed conduction[23] of the second P wave. Obviously this sinus impulse penetrated to the site of the nodal pacemaker postponing its spontaneous discharge, but then failed to reach the ventricles.

3. In none of these 3 records (nor in any other of the patient's records) was there evidence of A-V block. Prolongation of the P-R of the captures on 4-4, as well as the failure of an attempted capture to be completed on 4-11, are attributable to a normal state of relative refractoriness of A-V junctional tissues early in the nodal cycle. Thus, in this instance of acute rheumatic fever, selective involvement of A-V nodal rhythmicity, without any impairment of conductivity is clearly demonstrated.

Results and Discussion

Electrocardiographic Features of Nonparoxysmal A-V Nodal Tachycardia

Like any type of subatrial rhythm, nonparoxysmal nodal tachycardia may lead to retrograde activation of the atria provided the rate of discharge of the ectopic pacemaker exceeds the rate of the primary one and the retrograde conduction time through the A-V junction is short. This may be the case when the ectopic focus is located close to the atria, in the upper portion of the A-V node, but our material suggests that this is uncommon. Retrograde P waves were encountered in only 4 of the 30 cases (nos. 16, and 28–30 of table 1) and one of them is illustrated in figure 1 as an example of the mode of onset and termination of a nonparoxysmal nodal tachycardia. In this instance the transition of one rhythm into the other with interposition of atrial fusion beats superficially resembles a condition known as "wandering pacemaker." However, the latter is induced characteristically by slowing of the primary pacemaker whereas here the "shift in command" takes place as both sinus and nodal pacemaker speed up simultaneously, though to a different extent.

The usual consequence of a nonparoxysmal nodal tachycardia is 1 (or more) of the varieties (3) of A-V dissociation (figs. 2–5). The type of dissociation, whether persistent or intermittent on the one hand, and complete or incomplete on the other, will depend on the degree of enhancement of the nodal rate relative to the rate of the atria and on the state of refractoriness of the A-V junctional tissues.[9]

Since in a nonparoxysmal nodal tachycardia the limits of acceleration (70–130) of nodal impulse formation coincide with the range of ordinary sinus rhythms, an approximation or equalization of the timing of impulses of the 2 pacemakers is a common occurrence. It may take place during normal sinus rates (fig. 4) as well as during a sinus tachycardia (fig. 4). If the sinus rate is regular the dissociation will persist throughout the duration of the ectopic rhythm; in the presence of a sinus arrhythmia it may become manifest in an intermittent form, that is only during the slower phases of the sinus action (figs. 3 and 5). If under any of these circumstances the ectopic rate closely approaches or actually equals that of the sinus pacemaker the dissociation will become *complete* (fig. 3); then the independence of atrial and ventricular beating can be accounted for entirely on the basis of normal states of refractoriness in the A-V junction or, in other words, by persistent simple A-V interference[3] of the 2 impulses. If, on the other hand, the nodal acceleration exceeds the sinus rate, then *incomplete or complete* A-V dissociation may be the result. In the former, the occurrence of ventricular captures early in the nodal cycle and in a predictable manner may be considered evidence of normal A-V conductivity—and the physiologic handicap in the A-V junctional tissues to retrograde transmission of impulses[3, 19] may be invoked as the factor maintaining the dissociation (fig. 5). Should, however, under comparable conditions, ventricular captures fail to occur when expected, and the A-V dissociation be complete, the implication of a concomitant A-V block prolonging A-V refractoriness becomes inescapable. An excellent example of transition from one to the other of these 2 conditions is presented in figure 4.

Of course a nonparoxysmal nodal tachycardia can develop in the presence of atrial fibrillation[20] or flutter, and this can also lead to A-V dissociation. In our material this occurred in

about one third of instances in which the ectopic rhythm was attributable to digitalis medication (table 1). One instance is exemplified by figure 2, others have been illustrated elsewhere.[3] Similar cases have apparently been considered as instances of "complete A-V block."[18] While it is true that a nonparoxysmal nodal tachycardia in combination with rapid atrial rhythms usually leads to completely independent atrial and ventricular action, this independence is per se no proof that A-V conductivity is totally blocked. Complete A-V dissociation under such circumstances can, in our opinion, result from: the inability of retrograde nodal impulses to activate atria that are in a state of fibrillation, and the contribution of these accelerated retrograde nodal impulses to the state of refractoriness of the A-V junction, over and above the refractoriness induced by the rapid impulses of atrial fibrillation (or flutter). Sometimes preservation of A-V conductivity can actually be demonstrated in the form of ventricular captures effected by occasional atrial fibrillation impulses traversing the A-V junction.[3, 20]

The identification of ventricular captures in an A-V dissociation induced by a nonparoxysmal nodal tachycardia may require meticulous measurements. As a rule their occurrence can be presumed whenever single, or several successive, early beats are found in an otherwise regular ectopic ventricular action. Such "premature" conducted complexes may precisely resemble the dominant ectopic beats, or the 2 may differ in shape and QRS duration due to an aberrant intraventricular spread of the conducted or of the ectopic impulses.[21] If the atria respond to sinus impulses and P waves can be recognized, the diagnosis of ventricular captures can be fortified by the demonstration of a typical inverse relationship between R-P and P-R intervals. Such data can then be used to estimate the duration of the absolute and relative refractory phases of the A-V junction in the individual case and to rule out the presence of A-V block or to determine its type and degree.[3]

Exceptionally, however, conduction of sinus impulses in predominant A-V dissociation may be recognized on the basis of sudden lengthening, rather than shortening, of an R-R interval. This will be the case when a sinus impulse after entering the A-V junction penetrates to the site of the nodal pacemaker and, preceding the spontaneous nodal discharge, interrupts the nodal cycle, but is then retarded (figs. 4 and 5) or completely stopped (fig. 5) in its further spread to the ventricles. The latter event, representing an attempted but not completed capture, has been described previously;[9, 22, 23] the former, which may be termed "delayed capture," has to our knowledge not been reported as yet.

Clinical Significance of Nonparoxysmal A-V Nodal Tachycardia

Whereas paroxysmal acceleration of nodal impulse formation occurs, as a rule, in individuals free from demonstrable cardiovascular abnormalities, this is the exception for the nonparoxysmal variety. Thus, only in 2 of our cases (nos. 28 and 29) was clinical cardiac pathology not detected. In more than half of the cases nonparoxysmal nodal tachycardia was encountered as a consequence of digitalis therapy for congestive heart failure; in the others it occurred either in the course of acute rheumatic fever or in the early stages of posterior wall infarction. This apparent predilection for these conditions is not surprising considering the very frequent occurrence of another manifestation of A-V nodal pathology, namely A-V block in all 3 of these states.

However, disorders of the 2 functions of the A-V node, transmission and formation of impulses, need not be associated. Our material shows both their combined as well as their independent development. The predominant feature in digitalis-induced nonparoxysmal nodal tachycardia was its association with A-V block. Contrariwise, the majority of cases with acute rheumatic fever or posterior wall infarction developed A-V dissociation due to nonparoxysmal nodal tachycardia without any evidence of impaired A-V conductivity, even in serial records. Such observations contradict a recent statement[24] that "A-V dissociation and nodal rhythm in acute rheumatic fever have never been described without preceding or following periods of fixed P-R prolongation."

Hence, the interesting hypothetical concept concerning the mechanism of A-V arrhythmias developed on this basis[24] seems to have no validity from the clinical standpoint.

The clinical importance of a nonparoxysmal nodal tachycardia varies depending on circumstances of its development. In cases of recent posterior wall infarction it lasted for only a few days and, although 1 patient (no. 27) died after the onset of the nodal acceleration, it could not be considered an unfavorable sign of the condition of the patient at the time or of the final outcome of the attack. Indeed, the moderate acceleration of the ventricular rate with the onset of the ectopic rhythm may sometimes relieve symptoms caused by marked bradycardia, so common in the early stages of posterior wall infarction, which results from a pronounced slowing of the sinus rate or from a complicating advanced A-V block.

In acute rheumatic fever, on the other hand, a nonparoxysmal nodal tachycardia is a highly significant event, since it may represent the only electrocardiographic evidence of myocardial involvement, particularly in cases that do not develop an A-V block at any time. While it is true that nonparoxysmal nodal tachycardia is far less frequent than a simple P-R prolongation, it occurs more often than higher degrees of A-V block.[25-27] Like the P-R prolongation, nonparoxysmal nodal tachycardia is closely linked to other signs of rheumatic activity and may be easily missed without daily electrocardiograms (fig. 5). It may occur only at the peak of activity (fig. 4) or it may persist into and subside gradually during the stage of recovery (fig. 5). Contrary to P-R prolongation nonparoxysmal nodal tachycardia is a transient phenomenon that does not outlast the clinical and laboratory evidence of rheumatic activity.

Perhaps most important from the clinical standpoint is the recognition of a nonparoxysmal nodal tachycardia induced by digitalis medication because of its frequency, because of its bearing on the therapeutic results, and because it is one of the manifestations of digitalis excess. Some of the problems involved are illustrated in fig. 3, which reveals the gradual acceleration of nodal activity—and ventricular rate—in a patient kept on a small maintenance dose of digitalis, as well as its deceleration after discontinuation of the medication. If, as in this instance, nonparoxysmal nodal tachycardia develops during atrial fibrillation and causes complete A-V dissociation, the ensuing regularization of the ventricular action can be readily mistaken at the bedside for conversion to sinus rhythm unless it is clarified by an electrocardiogram. Should the ectopic rhythm remain unrecognized and medication be continued, the result may be further "paradoxical" acceleration of the ventricular rate, a development that not only defeats the purposes of digitalis therapy but may lead from the stage of "digitalis excess" into one of actual digitalis intoxication.[28]

Conclusions and Summary

Enhanced rhythmicity of the A-V node is manifested in clinical electrocardiography in a paroxysmal and nonparoxysmal form. These 2 types of rapid ectopic rhythms differ not only in the mode of onset and of termination but also in the degree of acceleration and especially in their clinical significance.

Although a nonparoxysmal A-V nodal tachycardia may cause retrograde activation of the atria it usually leads to A-V dissociation. Depending on the type of atrial activity, the relationship between atrial and ventricular rates and the state of refractoriness of the A-V junctional tissues, the A-V dissociation may be persistent or intermittent, and complete or incomplete. Incomplete dissociation becomes evident by sudden shortening, or lengthening, of some of the otherwise regular ventricular cycles.

Nonparoxysmal A-V nodal tachycardia is found predominantly in acute pathologic conditions known to cause moderate or advanced degrees of A-V block, in particular digitalis excess, acute rheumatic fever, and recent posterior wall infarction. It would therefore appear that both are manifestations of pathologic processes preferentially involving the A-V node. Sometimes only the property of impulse conduction is affected, sometimes that of impulse formation, and sometimes both these

functions are involved simultaneously, or successively.

Nonparoxysmal A-V nodal tachycardia represents an electrocardiographic entity with multiple facets and is an important factor to be considered in the assessment of digitalis excess and of rheumatic activity.

Summario in Interlingua

Rhythmicitate accelerate del nodo atrio-ventricular es manifeste in le electrocardiographia in un forma paroxysmic e in un forma nonparoxysmic. Iste 2 typos de rapide rhythmo ectopic differe non solmente in lor modo de declaration e de termination sed etiam in le grado del acceleration e specialmente in lor signification clinic.

Ben que le nonparoxysmic tachycardia a nodo atrio-ventricular pote effectuar un activation retrograde del atrios, illo resulta usualmente in dissociation atrio-ventricular. Secundo le typo de activitate atrial, secundo le relation inter le frequentias atrial e ventricular, e secundo le stato de refractorietate del tessuto de junction atrio-ventricular, le dissociation atrio-ventricular pote esser persistente o intermittente, complete o incomplete. Incomplete dissociation deveni evidente per un subitanee accurtation o prolongation de certes del alteremente regular cyclos ventricular.

Nonparoxysmic tachycardia a nodo atrio-ventricular se trova predominantemente in acute conditiones pathologic que es cognoscitemente capace a causar moderate o avantiate grados de bloco atrio-ventricular, specialmente excessos de digitalis, acute febre rheumatic, e recente infarcimentos del pariete posterior. Per consequente il pare que ambes es manifestationes de processos pathologic que affice per preferentia le nodo atrio-ventricular. A vices, solmente le proprietate del conduction de impulsos es afficite, a vices le proprietate del formation de impulsos, e a vices ambe iste proprietates es afficite—simultanee—o successivemente.

Nonparoxysmic tachycardia a nodo atrio-ventricular representa un entitate electrocardiographic con multiple facettas e es un factor importante que non debe esser negligite in le evalutation de excessos de digitalis e de activitate rheumatic.

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Black-Schaffer, B.: Infantile Endocardial Fibroelastosis. A Suggested Etiology. Arch. Path. **63:** 281 (March), 1957.

The current interpretations of endocardial fibroelastosis as a genetically determined congenital lesion or a consequence of hypoxemia are examined in the light of the pathologic physiology of cardiac structure and by application of Lapace's law of hydrostatics. Since it has been repeatedly demonstrated that mechanical forces may exert an influence on the genesis and development of the elastica, especially if those forces are rhythmic and fluctuating, it would seem probable that the great tensions that are cyclically accentuated in the endocardium of the dilated heart would be good reason for the genesis of endocardial fibroelastosis. Since the hypothesis here advanced is based upon mechanical considerations, cardiomegaly with endocardial fibroelastosis may develop in utero, given the appropriate constellation of force relationships. It is significant, however, that unequivocal examples of congenital idiopathic cardiomegaly with endocardial fibroelastosis are extremely rare. Anoxemia cannot be a significant factor except terminally, since the almost complete and uniform absence of recognizable ischemic myocardial injury in these huge hearts excluded it as an etiologic factor.

The material studied consisted of examples of idiopathic cardiomegaly with endocardial fibroelastosis, anomalous left coronary artery arising from the pulmonary artery, miniature left ventricle resulting presumably from premature closure or stenosis of the foramen ovale, and miniature right ventricle. The presence of endocardial fibroelastosis can be explained on a mechanical basis in each instance; and furthermore, the theory appears to fit the peculiarities of cardiac structure and function found in these anomalies.

MAXWELL

Left Heart Catheterization by the Transbronchial Route

Technic and Applications in Physiologic and Diagnostic Investigations

By Andrew G. Morrow, M.D., F.A.C.S., Eugene Braunwald, M.D., J. Alex Haller, Jr., M.D., and Edward H. Sharp, M.D.

Left heart catheterization is proving of increasing importance in the study of a variety of congenital and acquired cardiovascular defects. More than 500 left heart catheterizations have been performed by the transbronchial method without death or serious sequelae. This technic and its usefulness in clinical investigation and in the assessment of valvular heart disease are described.

THE development and application of technics for catheterization of the left side of the heart are proving of increasing importance in the study of patients with many types of cardiovascular disease. Two methods of left atrial puncture are commonly employed. The transbronchial method, devised by Allison and Linden[1, 2] and Facquet et al.[3] and the posterior percutaneous route employed first by Bjork et al.[4] Since 1953 more than 500 transbronchial left heart catheterizations have been performed at the National Heart Institute where the technic has been extended to permit the passage of a catheter into the left ventricle. The present report summarizes our experience with the method and the details of technic and instrumentation that have evolved.

Anatomic Considerations

When the left atrium is of normal size, as in many forms of congenital heart disease and in most patients with isolated aortic valve disease, it lies below and anterior to the carina and main bronchi. The space between the carina and left atrium is occupied only by mediastinal fat and areolar tissue. Irrespective of the degree of left atrial enlargement, the portion of the atrium adjacent to the left bronchus is, in most instances, extrapericardial. The anatomic relations of the normal-sized left atrium to the bronchial tree are shown in figure 1. As the left atrium enlarges, as in mitral valvular disease, it extends in a posterior and superior direction and may come in contact with or even elevate and compress the left main bronchus. The altered relationships of the left atrium to the bronchi in mitral valve disease are illustrated in figure 2.

Equipment and Instrumentation

A standard 7- or 8-mm. bronchoscope is used in adult patients. The transbronchial needle will pass through a 5-mm. full-lumen bronchoscope and an instrument of this size is used in children.

The needle used for bronchoscopic catheterization is illustrated schematically in figure 3.* It consists of an outer tube of stainless steel tubing 4.5 mm. in outside diameter and 50 cm. long, which divides proximally into 2 limbs, each fitted with a female Luer connector. The needle itself is constructed of 17-gage stainless steel tubing and a sleeve 6 cm. from its tip threads into the distal end of the outer tube. The needle point is ground to a 45° bevel and the edges are carefully smoothed to prevent the catheter from being caught or cut. The portion of the needle projecting from the outer tube represents the effective penetrating length of the needle. A safety collar is soldered to the needle just distal to its connection with the outer tube. The remainder of the needle, when assembled, lies inside the outer tube and its proximal end terminates in a funnel-shaped tip that lies within the upper Luer connector of the outer tube. Holes are placed at intervals along the portion of the needle within the outer tube to permit the evacuation of all air from the space between the outer tube and needle and to allow the transmission of pressure pulses from the needle tip to the outer tube.

Prior to use the needle and outer tube are assembled and the upper proximal limb of the outer tube is closed with a needle plug. The instrument is sterilized by autoclaving it. The lower proximal limb of the outer tube is connected via a 3-way stopcock to a Statham P23A transducer filled with 70 per cent alcohol.

The catheter ordinarily employed is made of poly-

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* Manufactured by the Becton-Dickinson Co., Rutherford, N. J.

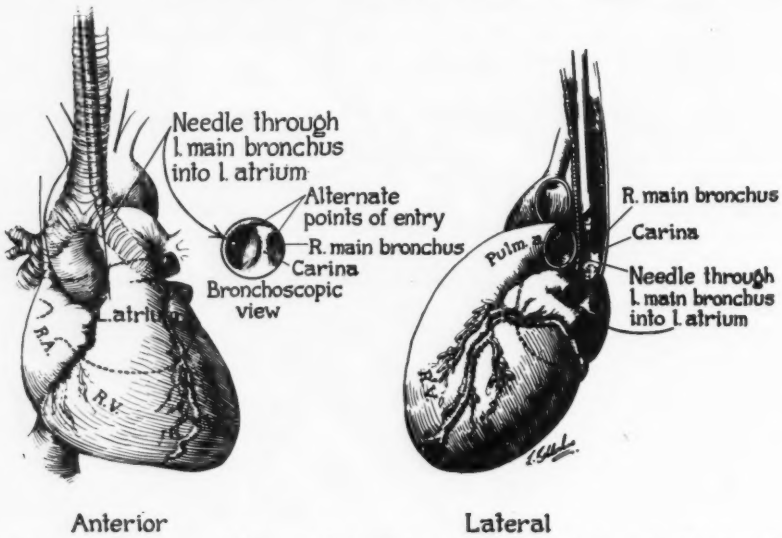

FIG. 1. Anatomic relations of the normal-sized left atrium to the main bronchi. The sites of bronchial puncture are indicated.

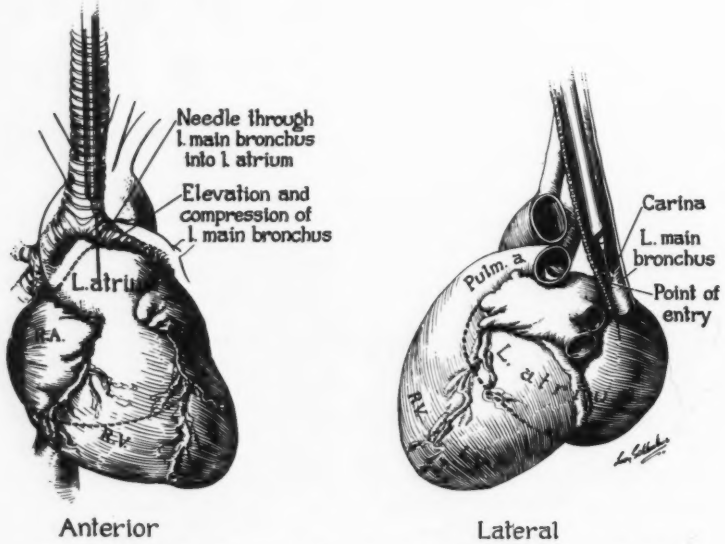

FIG. 2. Anatomic relations of the enlarged left atrium to the main bronchi.

ethylene. (Clay-Adams, size PE 50, 0.58 mm. I.D., 0.96 mm. O.D.). It is 100 cm. in length and its proximal end is flanged with heat and fitted with a screw adapter (Clay-Adams A-2625), which does not compromise its lumen. It is sterilized by soaking in aqueous benzalkonium chloride 1 per cent. This catheter is attached, via a 3-day stopcock to a Statham P23D transducer. The natural frequency of this catheter-gage system is approximately 20 c.p.s.

Both photographic and direct-writing recorders have been used in these studies. A photographic system has been found preferable because of greater paper width and the advantages of simultaneous superimposed pressure records. The records reproduced were made with a multichannel cathode-ray instrument. A 2-channel oscilloscope is used for visual monitoring of the electrocardiogram and pressure pulse from the needle or catheter.

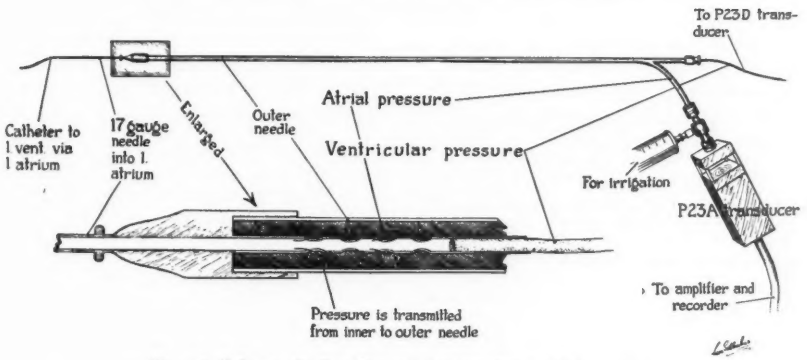

FIG. 3. Schematic drawing of the transbronchial needle.

PROCEDURE

The patient is prepared for the procedure by fasting for 6 hours. Intramuscular penicillin is given the evening before the catheterization and injections are repeated the following 2 mornings. Demerol, scopolamine, and an oral barbiturate are given 40 to 60 minutes beforehand. The larynx and trachea are anesthetized by the injection of 3 ml. of 1 per cent tetracaine hydrochloride (Pontocaine) through the cricothyroid membrane. Additional anesthetic is then sprayed into the hypopharynx. Electrocardiographic electrodes and a phonocardiograph microphone are attached to the patient.

All air is expelled by flushing the needle and outer tube with 30 to 40 ml. of sterile heparinized saline solution injected through the stopcock. The assembly is then clamped with the fluid-filled needle horizontal and in communication with the transducer. The transducer is then balanced. A convenient sensitivity setting has been found to be 2 mm. of paper deflection per mm. Hg pressure.

The bronchoscope is introduced, advanced to the carina, and additional Pontocaine is sprayed into the first portion of the left bronchus. In most instances a point on the anterior wall of the left bronchus 1 to 2 cm. from the carina is selected for puncture. If the left atrium is of normal size, a conscious effort must be made to direct the needle as far anteriorly as possible. This is facilitated by rotation of the bronchoscope so that its bevel lies posteriorly. The saline filled needle is then introduced into the bronchoscope, the transducer serving as a convenient handle. A zero or baseline pressure tracing is recorded before the needle pierces the bronchial mucosa and while it is in the axis of its eventual penetration. This baseline remains valid if the angle of the needle to the horizontal remains unchanged. The needle is then inserted through the bronchus for its full length and its entry into the left atrium can usually be felt as a sudden lessening of resistance. The needle is immediately irrigated with sterile saline solution and the left atrial pressure curve ordinarily appears immediately upon the monitoring oscilloscope. If the puncture is unsuccessful it is usually because the needle was not directed far enough anteriorly. It is withdrawn, irrigated, and inserted again after the baseline has again been recorded.

Left atrial pressure is recorded during several respiratory cycles and during a period of apnea in midinspiration. Mean pressure is determined by electric damping or by planimetric integration of the curves.

After left atrial pressure has been recorded via the needle, the catheter is filled with heparinized saline and its tip held at the level of the midaxillary line where the zero or baseline pressure is recorded. The catheter is handled by a gloved assistant to maintain sterility. The needle plug is then removed by the endoscopist and the assistant passes the catheter into the proximal end of the needle. The catheter is advanced by the assistant for about 50 cm. and it is then handled by the ungloved endoscopist. Thus, the portion of the catheter that enters the heart remains sterile. The pressure at the catheter tip is monitored by an oscilloscope, the face of which is visible to the endoscopist. The catheter is slowly advanced into the atrium and occasionally irrigated with saline. When the mitral leaflets are mobile their movement can often be felt on the catheter tip just before it enters the ventricle. The entrance of the catheter into the ventricle is signaled by a change in the oscilloscopic tracing from an atrial to a ventricular pressure pulse. A record of ventricular pressure is made and recording is continued as the catheter tip is slowly withdrawn into the left atrium. Catheterization of the ventricle and pull-out tracings are usually repeated several times after which the catheter is withdrawn, the needle plug reinserted, and the needle removed. The puncture site is inspected, residual mucus and blood aspirated, and the bronchoscope withdrawn.

Ordinarily, no difficulty is encountered in passing the catheter across the mitral valve. An exception is the presence of gross mitral insufficiency when the catheter may enter the ventricle only to be washed

back into the atrium with ventricular systole. A stiffer catheter of extruded Nylon may then be substituted for the flexible polyethylene one.

In our patients an attempt has been made to pass the catheter from the left ventricle into the aorta only in congenital aortic stenosis where a subvalvular obstruction may exist. Ordinarily, the aortic valve gradient is determined by simultaneous measurement of brachial artery or central aortic pressure while the transbronchial catheter is in the left ventricle. The details of central aortic catheterization are described elsewhere.[5]

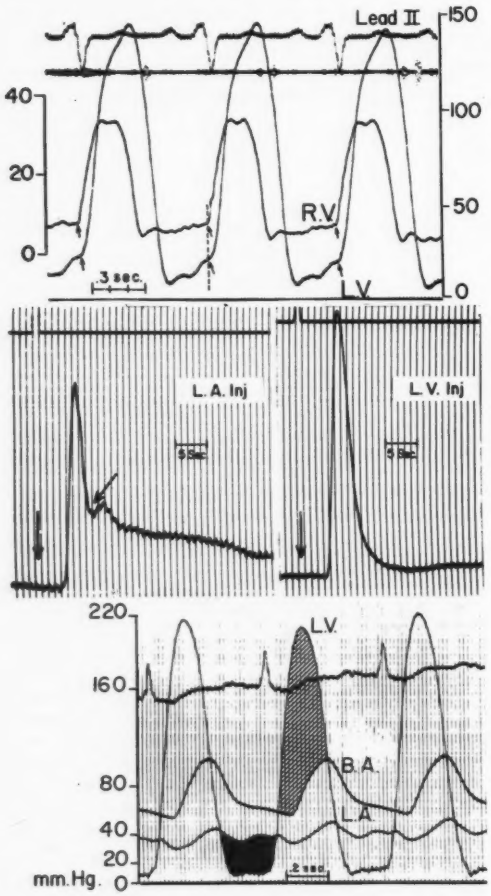

FIG. 4 *Top*. Simultaneous left and right ventricular pressure pulses in a patient with the electrocardiographic configuration of complete left bundle-branch block. The onset of ventricular contraction is indicated. Contrary to expectation there is no delay in the onset of left ventricular contraction.

FIG. 5 *Middle*. Indicator dilution curves recorded from the femoral artery following left atrial and left ventricular injections in a patient with an interatrial septal defect. In the curve resulting from left atrial injection, the fraction of the dye that was shunted across the defect and through the pulmonary circulation interrupts the descending limb of the primary curve. The curve resulting from the left ventricular injection is normal, indicating the absence of a left-to-right shunt distal to a competent mitral valve. Midpoint of injection is indicated by the vertical arrows. Time intervals are 1.0 second.

FIG. 6 *Bottom*. Pressures recorded simultaneously from the left atrium, left ventricle, and brachial artery in a patient with combined mitral and aortic stenosis. The stippled area shows the mitral valve filling pressure gradient and the diagonally cross-hatched area the aortic valve gradient. Left atrial pressure was recorded in this instance by a second needle puncture while the catheter remained in the left ventricle.

RESULTS

Transbronchial puncture of the left atrium has been performed more than 500 times in patients with congenital or acquired heart disease. The procedure was also carried out in 15 patients with normal hearts undergoing bronchoscopy for other reasons. In 4 patients abnormalities of the mouth or jaw prevented introduction of the bronchoscope. In an occasional patient with a left atrium of normal size the puncture was unsuccessful. There were no deaths in the series. There have been no instances of infection, pneumothorax, mediastinal emphysema, or pericardial tamponade. In many patients the sputum was blood-streaked for several hours following the procedure but there was never significant hemoptysis. No difficulty has been encountered with withdrawal of the catheter through the needle and the catheter was never cut. In some of the patients undergoing operation after the procedure the pericardial fluid was found to be xanthochromic or blood-stained. In none of these was the pericardial fluid increased in quantity or under pressure. The bronchoscopy and catheterization can usually be completed in 5 to 10 minutes although in selected patients continuous records have been made for 45 minutes or longer.

In this clinic, left heart catheterization is employed in 2 general areas of investigation. The first of these is concerned with the study of a variety of clinical hemodynamic problems.

Among these have been: (1) the determination of the sequence of ventricular contraction in bundle-branch block[6] (fig. 4); (2) the study of pressure-volume relationships in the left atrium[7] and left ventricle[8]; (3) the influence of increased central blood volume on left heart filling pressures; (4) the effect of acutely increased peripheral resistance on the left atrial pressure contour in mitral valve disease[9]; (5) indicator dilution curves with left heart injection in the precise localization of left-to-right shunts and the detection of mitral and aortic insufficiency[10] (fig. 5).

The second area of usefulness has been the clinical evaluation of patients with valvular heart disease. Attention has been focused upon: (1) the evaluation of the left atrial pressure pulse contour in differentiating mitral stenosis and mitral insufficiency[11]; (2) determination of the diastolic gradient across the mitral valve in the selection of patients for mitral commissurotomy and in the assessment of the hemodynamic results of the operation (fig. 6); (3) measurement of the systolic gradient across the aortic valve in the selection and postoperative evaluation of patients with aortic stenosis (fig. 6); (4) determination of the hemodynamically predominant lesion in patients with combined valvular lesions.

Discussion

Perhaps the most essential requirement for successful transbronchial left heart catheterization is the participation of an experienced bronchoscopist. Good topical anesthesia and a smooth introduction of the instrument are mandatory. The procedure has been carried out even in severely ill patients when careful attention has been directed to their general preparation and the timing and dosage of preanesthetic drugs. The presence of severe tachycardia or frequent ventricular extrasystoles has usually constituted a contraindication to the procedure. The method lends itself well to serial studies in the same patient. Numerous patients have been catheterized 3 or more times and 1 individual has had 7 transbronchial left heart catheterizations.

When the decision is made to employ any procedure extensively in clinical investigation first consideration must be given to its safety. In this regard, some comparison of the transbronchial and percutaneous methods of left heart catheterization would seem in order. Although we have not employed percutaneous puncture of the left atrium, that method has been widely adopted in this country. Bjork and colleagues[12] have recently reported their experiences with percutaneous left heart catheterization in 167 patients. Of these, 39 also had angiocardiographic examinations with left heart injections. There was a total of 14 major complications. Of 2 patients who developed cardiac tamponade, 1 died. Cardiotomy was required on 2 occasions for removal of a knotted or cut catheter. Bjork therefore concluded that left heart catheterization should be performed only when the information obtained by the procedure was required in making a decision as to operation. Goldberg[13] has performed 450 left heart catheterizations by the percutaneous method. In this series there were 5 deaths. Four patients required cardiotomy for knotted catheters; 5 had significant hemopericardium. There was 1 death resulting from hemopericardium among the 75 percutaneous left heart catheterizations performed by Wood at the Mayo Clinic.[14] In a series of 40 percutaneous left heart catheterizations performed by Blakemore, 1 of 2 patients who developed cardiac tamponade died.[15]

No deaths or significant complications occurred in the course of the 500 transbronchial catheterizations in the present series. Recent communication from Professor Allison,[16] Dr. Facquet,[17] and Mr. Geoffrey Wooler[18] indicate that they have performed transbronchial puncture of the left atrium in 160, 200, and 211 patients respectively. No death or serious complication occurred in any of these series. Thus, in a combined experience of over 1,000 transbronchial left heart catheterizations in 3 clinics, the procedure has never resulted in death or serious sequelae.

In transbronchial puncture of the left atrium the needle does not ordinarily traverse the free pericardial space. This is thought to account in large measure for the absence of complications due to intrapericardial bleeding and tamponade. In paravertebral puncture of the left

atrium the needle must pass through the free pericardium and in relation to the lung, aorta, azygos vein, and esophagus. Although a small pneumothorax or hemothorax is of little importance ordinarily, either would seem undesirable in a patient ill with heart disease. As the safety of the transbronchial method has become progressively apparent we have felt justified in using the technic as a clinical investigative tool.

With a bronchoscope in the trachea most patients cannot be considered to be in a steady basal state, and valid measurement of the cardiac output cannot be made by the direct Fick method. Also, during bronchoscopy studies involving exercise are impractical. These objections to the transbronchial method have been largely obviated. Cardiac output is determined at the time of bronchoscopy by the indicator dilution method. The validity of the technic and instrumentation employed had been previously established.[19] Hemodynamic observations are made with the bronchoscope in place, after which the needle and bronchoscope are withdrawn and the catheter is left in the atrium or ventricle. Measurements of pressures and cardiac output are then repeated after the patient has returned to a more basal state. Although the determination of cardiac output by the Fick method is possible, simultaneously with the measurement of left heart pressures by the percutaneous method, it has not as yet been demonstrated that a basal steady state is readily achieved with this technic.

Summary

The technic and instrumentation of left heart catheterization by the transbronchial route are described. More than 500 catheterizations have been performed at the National Heart Institute without mortality or serious morbidity. The procedure has been found useful in a variety of clinical investigations and in the preoperative selection and postoperative assessment of patients with valvular heart disease.

Acknowledgment

The authors are indebted to a number of individuals who have participated in the studies described. Dr. Donald L. Fry and Mrs. Estelle K. Cohen contributed much in the field of instrumentation and recording. Dr. Robert P. Grant, Chief of the Section on Cardiovascular Hemodynamics, examined most of the patients who were catheterized and was of great help in their clinical assessment. One of us (A.G.M.) had the privilege of working with Mr. P. R. Allison, F.R.C.S., presently Nuffield Professor of Surgery, Oxford, and former Chief of the Thoracic Surgery Department, Leeds General Infirmary. The method of left heart catheterization described is an extension of the technic developed in his unit.

Summario in Interlingua

Le technica e instrumentation de catheterisation sinistro-cardiac a via transbronchial es describite. Plus que 500 catheterisationes ha essite executate al Instituto National del Corde sin mortalitate e sin serie morbiditate. Le technica se ha provate utile in un varietate de investigationes clinic e in le selection preoperatori e le evaluation postoperatori de patientes con morbo de valvula cardiac.

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Odier, J., Montouchet, M., and Duchosal, P. W.: A Spatial Study of the Premature Component in the Syndrome of Wolff-Parkinson-White. Cardiologia **20:** 182 (March), 1957.

The authors present the results of vectorcardiographic studies in 13 patients with the Wolff-Parkinson-White syndrome with particular consideration of the anomalous (premature) component of the QRS complex. The respective portion of the ventricular loop has often a complex appearance, not evident in the scalar leads, and points always anteriorly and to the left. Its duration varies between 0.04 and 0.13 second. If the entire thorax is explored by unipolar (scalar) leads, mirror-image patterns of the abnormal deflection can be obtained in diametrically opposed chest positions. The authors conclude on the basis of this analysis that the preexcitation component corresponds to forces different from the normal initial forces and that they occur in a limited and well-defined area, remote from normal conduction pathways. The point of origin seems to be somewhere near the electric center of the heart, rather than in some peripheral portion of the ventricular myocardium.

PICK

Diverticulum of the Pericardium

With Observations on Mode of Development

By HERBERT C. MAIER, M.D.

A diverticulum of the pericardium can often be confused with other lesions of the heart and great vessels as well as mediastinal cysts and other masses. Pericardial effusion, sometimes associated with heart lesions causing cardiac enlargement, is a frequent factor in producing diverticular formation. The mode of development of a pericardial diverticulum is better appreciated when certain features of the anatomic structure of the parietal pericardium are understood. Two cases of pericardial diverticulum that illustrate the etiologic, clinical, and roentgen features of the lesion are presented.

A DIVERTICULUM of the pericardium may develop secondary to cardiac disease and pericardial effusion. When discovered on roentgen examination, the appearance may simulate cardiac or aortic aneurysm, vascular anomalies, cardiac and pericardial tumors, and mediastinal cysts. Since a diverticulum of the pericardium is rare, there has thus far been little opportunity to follow roentgenographically the evolution of the lesion over a period of years. Two cases of diverticulum of the pericardium herewith reported have provided some information concerning the mechanisms of development. The opinion has been expressed by some observers that localized weakness of the pericardium with an additional factor of pericardial distention by fluid was the usual responsible mechanism. One of our cases in which clinical and radiographic data were available over a period of years demonstrated this sequence of events after an attack of idiopathic pericarditis. The other case indicated the close relationship between pericardial diverticulum and the more common pleuropericardial cysts, which are of congenital origin.[1]

The mechanism of development of an acquired pericardial diverticulum is more readily understood when certain points related to the histology of the pericardium are appreciated. The parietal pericardium is a fibroserous sac that consists of an outer fibrous layer and an inner serous layer. The pericardium merges with the sheaths of the great vessels with the single exception of the inferior vena cava, which pierces the pericardium from below. The outer fibrous layer is strong and inelastic due to interlacing collagenous fibers. The serous or inner layer of the parietal pericardium has a smooth and glistening lining that is covered by mesothelium. After splitting the outer fibrous sheath one can separate the inner serous layer from it and thus demonstrate grossly the 2 layers. After separation of these 2 layers over a small area it is then possible to evaginate the inner serous lining through the defect in the outer fibrous covering. Thus one can demonstrate the mechanism by which a herniation of the inner serous layer may occur through a cleft or weak place in the outer fibrous layer. Since the inner serous lining is far more distensible than the outer fibrous covering, a protrusion of the thin inner layer could gradually produce an enlarging diverticulum as a result of increased intrapericardial pressure such as is caused by cardiac enlargement and pericardial effusion. Study of the pericardium at autopsy demonstrates some variation in the ease with which the parietal pericardium can be split into its 2 component layers. In some cases a cleavage plane can be readily established between the outer fibrous and inner serous layer over a considerable distance because only delicate fibers join the 2 layers. In other instances, especially in the atrophic pericardium of the aged, demonstration of the 2 layers is much less satisfactory. In some areas of the parietal pericardium the interlacing collagenous fibers of the outer layer are obviously unevenly distributed. It is in the potentially weak spaces between groups of fibers, especially near

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the roots of the great vessels, that the thin serous layer may bulge through when the intrapericardial pressure increases. The pericardial fluid can then distend the protruding serous layer so as to produce a gradually enlarging sac. Rarely a diverticulum may be produced by localized traction on a small area of pericardium.

It is stated in the literature that the wall of a pericardial diverticulum is similar to that of the pericardium but this does not appear to be entirely correct. Although on ordinary microscopic examination no striking difference in the appearance of the wall of a pericardial diverticulum and the normal parietal pericardium may be readily apparent, a macroscopic difference may be noted. The diverticulum does not possess the dense bands of collagen fibers that impart some degree of stiffness to the normal parietal pericardium. In contrast the diverticular sac is very flexible and flaccid. However, the wall of the diverticulum tends to be thicker than the serous layer of a normal pericardium. When a pericardial diverticulum is observed at operation, one notes the tendency of some pericardial fluid to flow back and forth between the pericardial sac and the diverticulum during phases of the cardiac cycle. This rhythmic distention of the herniating sac may well play a role in its gradual enlargement. The diverticulum readily varies in shape and size with changes in position of the patient. The sac usually hangs down from the site of communication with the pericardium and is often pear-shaped.

A critical review of the literature emphasizes the necessity of discarding from consideration those cases in which the diagnosis was not proved by autopsy or operation. There are some reports based only on radiologic findings that are not even suggestive of a pericardial diverticulum when considered in the light of recent surgical experience with mediastinal masses.[2-4] In other reports no distinction is made between diverticulum, localized pericardial effusion with regional protrusion, or localized perforation of the pericardium from a pathologic process such as tuberculosis.[5] Moreover, in some of the cases designated as diverticulum of the pericardium the sac with fluid did not communicate with the pericardial cavity but was merely attached to the pericardium. In recent years such pleuropericardial cysts have been recognized as relatively common lesions.[1] This discussion is concerned only with cases in which there is localized outpouching of the pericardium so as to form a sac that protrudes from the remainder of the pericardium and communicates with the pericardial cavity. Only a relatively small number of cases in this category are available for study in the collected literature.[6]

Cushing[5] reviewed the literature on diverticulum of the pericardium in 1937. Some of the 40 cases he listed were unproved pathologically or may not be true diverticula. Various cardiac or other abnormalities that tended to distend the pericardial sac were recorded in a considerable percentage of the proved cases. The diverticulum presented most often on the right side. In most instances details concerning the exact site of the diverticulum were lacking but the sites seemed to vary considerably; in a few cases the origin was stated as being at the base near the origin of the great vessels. The size and shape of the diverticulum as well as the width of the neck of the sac varied considerably. None was very large. Most were incidental findings at autopsy in adults. Reports of pericardial diverticula in the newborn and in infancy seem to be lacking,[7] if pleuropericardial cysts, which do not communicate with the pericardial cavity, are excluded.

The criteria of radiographic diagnosis of a pericardial diverticulum reported by Kienböck and Weiss[4] on the basis of largely unproved cases seem unacceptable, since similar roentgen shadows may occur with pleuropericardial cysts, lymphatic cysts, and serous cysts. The density on the roentgenogram produced by a pericardial diverticulum is inseparable from that of the cardiac silhouette. The shape and location of the abnormal shadow may vary widely, and there may be a considerable change in the shape with changes in respiration and position. Some such alterations in relation to the cardiac silhouette may make it difficult to distinguish the diverticular outline from other mediastinal structures. The only absolute roentgen sign of a pericardial diverticulum

other than with pneumopericardium is disappearance of, or conclusive evidence of diminution in the size of the cystic mass when the patient is so positioned, as in lateral recumbency, that the diverticulum lies above the pericardium. Then some of the fluid in the diverticulum may drain back into the pericardium. It is usually very difficult to be certain that the cystic lesion has changed its volume because a thin-walled cyst that is not tense can change its shape so markedly that it is impossible to tell whether the volume is altered, even when films are taken in several projections. Misinterpretation may also result from shifting of the cystic mass in relation to the cardiac silhouette, so that the abnormal density may be thought to have disappeared when it has merely shifted its position and become superimposed on the cardiac shadow. Even pericardial fat pads and lipomas can be confused with cystic lesions around the pericardium. Sometimes a diverticulum with a large free communication with the pericardium will not empty on change in position because the pear-shaped diverticulum with a long neck can shift the position of its lower bulbous portion so as to remain below the level of the opening into the pericardial sac. Also, if there is a very small communication between the diverticulum and the pericardial cavity, fluid will not readily drain from the diverticulum. A pericardial diverticulum might be conclusively diagnosed in some cases by pneumopericardium but such a diagnostic procedure would appear to be undesirable.

Pericardial diverticula are often asymptomatic.[8] Occasionally there is a complaint of vague discomfort in the thorax. In a few cases circulatory signs and symptoms such as dyspnea, dizziness, and slight cyanosis have been present that have disappeared postoperatively although the mechanism of their production was not apparent unless torsion of a long pedicle was responsible or unrecognized cardiac lesions were present. Physical examination and auscultation do not aid in establishing the diagnosis. Electrocardiograms are normal unless alterations are produced by cardiac or other pericardial disease.

Case Reports

Case 1. This 49-year-old man had a history of chest pain for 1 day in 1947 and at that time a definite pericardial friction rub had been heard by several observers. The chest roentgenogram had shown no abnormality or enlargement of the cardiac silhouette (fig. 1*A*) and the lung fields were clear. A diagnosis of idiopathic pericarditis was made by Dr. C. de la Chapelle. In 1952 another chest roentgenogram was taken, and at this time a small bulge was noted at the right cardiac border on the postero-anterior film. The cardiac silhouette also showed some enlargement as compared to the roentgenogram of 1947. The electrocardiogram was normal. Slight hypertension was present and the enlargement of the cardiac silhouette was thought to be related to the hypertension. A year later another chest film showed a definite increase in size of the abnormal shadow (fig. 1*B* and *C*) and operation was recommended. The patient remained free of pulmonary or chest symptoms. The mass was found to be definitely larger than it had been 15 months previously. At operation in July 1953 a large pear-shaped diverticulum of the pericardium having its origin in the region of the base of the aorta was found and resected. There was an increased amount of pericardial fluid present. The postoperative course was uneventful and the patient was discharged on the eighth postoperative day. A year after operation the patient was asymptomatic and feeling fine. Microscopic examination of the wall of the diverticulum revealed that it was composed of a small amount of fibrous connective tissue covered by a single layer of somewhat hyperplastic endothelial cells. There was a slight chronic inflammatory cellular infiltration as well as dilated thin-walled and congested blood vessels.

Comment. Preoperatively the lesion had been considered to be probably a thymic tumor because of its location. At that time it was erroneously assumed that a pericardial diverticulum would not be likely to make its appearance in a 49-year-old man who had no evidence of such a lesion on roentgenographic examination when he was 45 years old. At the time of operation it was noted that the pericardial fluid was increased in amount. The postoperative roentgenograms showed a definite decrease in the size of the cardiac silhouette, indicating that the increase had been due to an abnormal amount of pericardial fluid rather than to cardiac enlargement (fig. 1*D*). In retrospect it is thought that the increased pericardial fluid that followed the idiopathic pericarditis 6 years previously had resulted in the development of a pericardial diverticulum by gradual protrusion

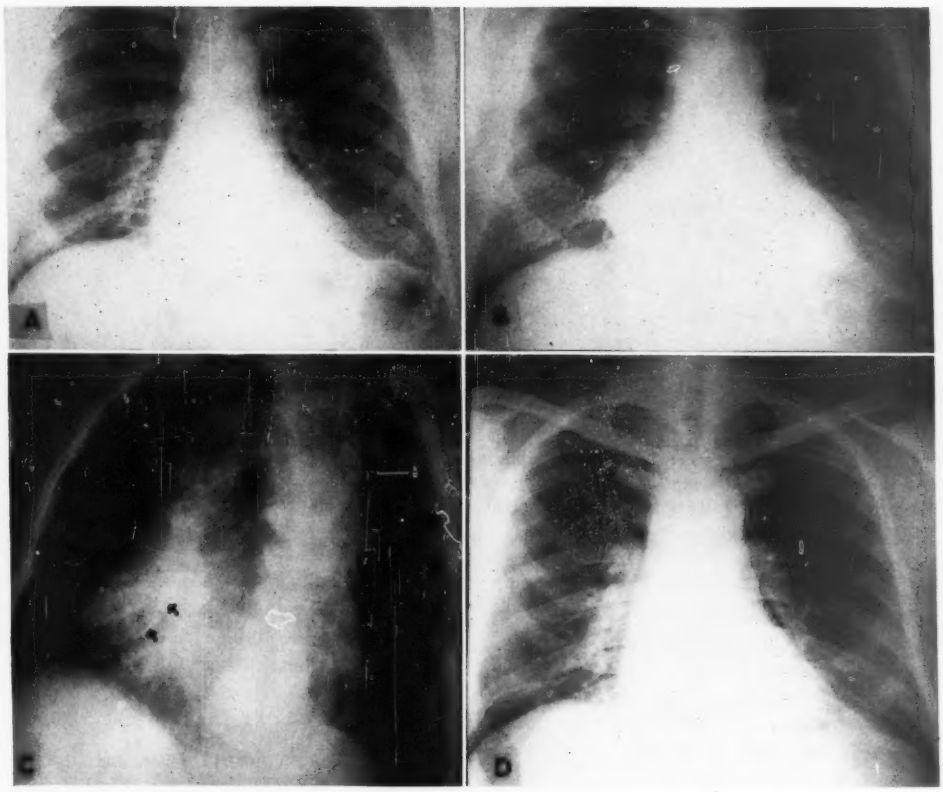

FIG. 1. *Case 1. A*. Roentgenogram at time of idiopathic pericarditis in 1947 showed normal cardiac silhouette. *B*. Roentgenogram 6½ years later showed generalized enlargement of the cardiac silhouette with a mass merging with the right lateral aspect of the heart. *C*. Oblique film reveals a mass with rounded lower border (indicated by arrows). The pear-shaped pericardial diverticulum hung down from its site of origin at the upper part of the pericardium. *D*. Postoperative roentgenogram reveals the cardiac silhouette to be smaller than preoperatively due to elimination of pericardial effusion. Pericardial diverticulum has been removed.

of the inner serous layer through a cleft in the fibrous bands of the outer layer.

Case 2. This 29-year-old man had occasional slight discomfort in the right anterior thoracic region. Roentgenograms of the chest showed a small mass of soft tissue or fluid density in the right supradiaphragmatic region adjacent to the cardiac border (fig. 2). The shape of the mass changed considerably with respiration; it was rounded on expiration and became elongated on inspiration. Barium studies of the alimentary tract revealed no evidence of a retrosternal diaphragmatic hernia.

At operation an irregular multilocular thin-walled cyst containing clear fluid was found attached to the anterolateral aspect of the pericardium. This was typical of a pleuropericardial cyst but a unique finding was a small pericardial diverticulum attached to the cyst by a fibrous strand. There was some excess fluid within the pericardium. The cyst and diverticulum were removed. The postoperative course was uneventful.

Comment. The lack of reports of cases of pericardial diverticulum in infancy and childhood and the frequent association of pericardial effusion or other factors that would distend the pericardial sac strongly suggest that most pericardial diverticula result from a gradual outpouching through a weak area in the pericardial wall. On the other hand, the close developmental association between pleuropericardial cysts, which are apparently usually of congenital origin, and abnormalities of pericar-

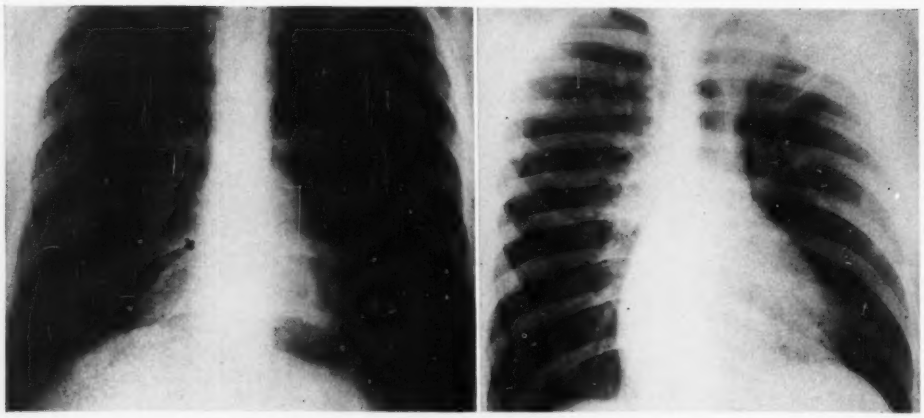

FIG. 2. *Case 2. Left.* Arrows indicate pleuropericardial cyst and pericardial diverticulum (indistinguishable from each other) at right cardiophrenic angle. A lateral film showed an anterior location of shadow. *Right.* Oblique film shows projection of density from the normal cardiac outline but merging with heart shadow. Radiologic distinction between a pleuropericardial and pericardial diverticulum not possible.

dial development seems evident. The pathologic findings in this case are of interest in this regard, since here a pleuropericardial cyst was intimately associated with the tip of a small diverticulum of the pericardium. Whether the development of this diverticulum was in part due to a traction effect of the cyst remains a moot question.

TREATMENT

It is questionable whether a pericardial diverticulum would usually require any therapy if a positive diagnosis could be established by radiologic and clinical criteria. At present it seems unjustified to assume that the radiologic features that have been described and discussed in the literature are sufficiently accurate to be considered diagnostic or reliable except in rare instances. Although alterations in the shape and contour of a pericardial diverticulum may be noted with changes in position or respiratory motion, similar variations may occur in pleuropericardial cysts and even other lesions. Therefore the management of the patient must be based on a realization of the limitations of radiographic differentiation of the large variety of mediastinal masses and vascular lesions that could simulate a pericardial diverticulum. Angiography will help to identify lesions of the heart and great vessels. When the radiographically detected mass is considered to be of nonvascular origin, thoracic exploration is advisable unless other conditions produce contraindications.

SUMMARY

The evidence concerning the mechanism of development of a diverticulum of the pericardium is discussed on the basis of 2 personally observed cases, some experimental autopsy observations, and an analysis of cases recorded in the literature. The development of a large diverticulum that was not roentgenographically demonstrable until some years after an attack of idiopathic pericarditis is recorded. Although congenital factors may play a predisposing role by providing a weak area in the parietal pericardium, an increase in intrapericardial pressure with pericardial effusion seems to be the important causative factor in many cases. A pericardial diverticulum usually results from the gradual stretching of a herniating portion of the inner serous layer of the parietal pericardium that bulges through the split or weakened outer fibrous layer of pericardium.

Evidence supporting the concept that pleuropericardial cysts and a pericardial diverticulum may have a common origin is indicated by a case in which both lesions were associated

together. However, congenital diverticulum of the pericardium seems to be extremely rare.

Summario in Interlingua

Le mechanismo del disveloppamento de diverticulos pericardial es discutite super le base de 2 personalmente observate casos, un serie de necroptic observationes experimental, e un analyse de casos reportate in le litteratura. Es reportate le disveloppamento de un grande diverticulo que non esseva demonstrabile per medios roentgenographic usque a plure annos post un attacco de pericarditis idiopathic. Ben que il es possibile que factores congenite exerce un rolo predispositori per provider un area de debilitate in le pericardio parietal, un augmento del pression intrapericardial con effusion pericardial pare esser le causa immediate in un grande numero de casos. Le processo usual es que un diverticulo pericardial resulta ab le tension gradual del portion herniate del strato serose interior del pericardio parietal que protrude a transverso le findite o debile strato fibrose exterior del pericardio.

Le conception que cystes pleuropericardial e diverticulos pericardial ha possibilemente le mesme origine es supportate per un caso in que le duo lesiones esseva associate. Tamen, diverticulos congenite del pericardio pare esser extrememente rar.

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Internal or common carotid artery ligation was performed in 63 patients because of intracranial aneurysm (44) or arteriovenous communication (19). Preoperative evaluation included angiography to determine the status both of the carotid and the basilar systems. If these were satisfactory, the patient's ability to withstand carotid ligation was then tested by high carotid compression for 10 minutes under electroencephalographic and electrocardiographic monitoring. Those individuals having an irritable carotid sinus were protected by the prior administration of 1.6 mg. of atropine. When carotid compression produced no untoward reaction, carotid ligation was followed by death in 2 patients both of whom were previously very ill, by transient hemparesis in 4 and by no significant side effects in the remainder.

Rogers

Significance of the Pulmonary Vascular Bed in Congenital Heart Disease

V. Lesions of the Left Side of the Heart Causing Obstruction of the Pulmonary Venous Return

By Charlotte Ferencz, M.D., and J. Francis Dammann, Jr., M.D.

A microscopic study was made of the lungs of 18 patients with congenital malformations of the heart in which there was obstruction of pulmonary venous drainage. Alterations in various components of the pulmonary vascular bed and of the lung parenchyma were described and correlated with the clinical course and the type of malformation present. A quantitative evaluation of the pulmonary arterial thickening was made by determining the lumen:wall ratio of small vessels. The anatomic alterations found in these children were compared to those of adults with acquired mitral stenosis.

LESIONS of the left side of the heart that impede pulmonary venous drainage lead to extensive anatomic and physiologic alterations in the lungs. Studies of the pulmonary changes in acquired mitral stenosis[1-7] indicate that the altered structure of the alveoli and of the pulmonary vascular bed serves at first as a protective mechanism, but eventually results in irreversible and detrimental changes. Such a progression has been observed in the adaptive pulmonary vascular changes in conjunction with congenital malformations of the heart in which a common systolic force ejects blood into the 2 circulations.[8-10]

The present report is concerned with the effect of "back pressure" on the lungs observed in 18 patients with congenital lesions that involved the left atrium, mitral valve, or pulmonary veins and caused obstruction of the pulmonary venous return. Although the malformations differed, in all instances the course of the fetal circulation was affected in such a way that the "back pressure" was present before birth. Its continued presence after birth interfered with the normal evolution of the pulmonary vascular bed from the fetal structure to the adult state.

The effect of an elevated pulmonary venous pressure that results from left heart failure in cases of aortic stenosis, coarctation of the aorta, endocardial fibroelastosis, etc., will be considered in a subsequent report. In such instances, pulmonary vascular evolution proceeds normally for a varying length of time and may even be completed before elevation of left ventricular filling pressure affects the lungs. Alterations produced in this group are, therefore, "acquired" and vary with the age of the patient and the severity and duration of the left ventricular failure. The present report is concerned with abnormalities of the heart in which impairment of pulmonary venous drainage influenced the pulmonary circulation before birth.

Methods

A microscopic study was made of the lungs of patients with malformations that affected the left side of the heart proximal to the mitral valve. Sections stained with hematoxylin and eosin and with elastic tissue stain were examined. Evidences of congestive failure and specific changes that involved the entire pulmonary vascular bed and lung parenchyma were evaluated and correlated with the clinical course and the type of malformation present. In order to allow an objective quantitation of the severity of the vascular changes, we have again used the method previously described[11] in which a numerical expression, denoted as the lumen:wall ratio, designates the characteristics of the small pulmonary vessels. This ratio was obtained by direct measurement of the thickness of the media and intima of the small pulmonary arteries. The sum of the intimal and medial thickness was multipled by 2 and divided into the measurement of the luminal diameter, thus giving the ratio of lumen size to wall thickness. The average reading of 10 small pulmonary vessels was

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taken as the lumen:wall ratio for that patient. This reading was compared with the lumen:wall ratios of normal individuals of corresponding ages.

Results

The malformations of the heart causing obstruction of the pulmonary venous return in 18 patients are listed in table 1.

In 14 of the 18 patients the lesion that impeded pulmonary venous drainage was associated with other malformations of the heart. In most instances the usual clinical findings of the additional anomaly were modified adversely by this combination of lesions. Brief synopses of the clinical and anatomic findings are given in the appendix.

Microscopic examination of the lungs of these patients revealed extensive changes in all components of the pulmonary vascular bed and lung parenchyma. The alterations were similar in all instances. One patient with unilateral congenital pulmonary venous obstruction (case 18) showed, in addition, evidence of serious vascular injury that will be considered separately.

The muscular pulmonary arteries showed medial thickening; this was the most uniform and probably the earliest change (fig. 1). Hypertrophy of the smooth muscle and an increase in the elastic tissue accounted for the thickening. This was primarily responsible for the reduction of the lumen:wall ratio. Intimal thickening, usually eccentric, was noted in the large muscular arteries of approximately one third of the patients. It was moderately severe in 2 of the oldest children, but was not uniformly present in all vessels. In 3 instances, including the 2 patients just mentioned, intimal changes were also found in some of the smaller muscular pulmonary arteries.

The arterioles were thickened in every case (fig. 2). In the 2 newborn infants the narrow lumens were in accordance with the normal fetal pattern. Thickening of the arteriolar walls by concentric cellular proliferation was frequently seen in the older children, giving an "onion ring" appearance.[1] When the media was not clearly defined by the elastic laminae, it was often difficult to distinguish arterioles from small muscular arteries, but the thickening of the wall was uniformly present even in the smallest vessels.

Table 1.—*Malformations of the Heart in Eighteen Patients with Obstructions of the Pulmonary Venous Return*

Malformation	Case number
Cor triatriatum (double left atrium)	1
Congenital mitral stenosis	
Pure mitral stenosis	2
Mitral stenosis associated with	
ventricular septal defect	3
single ventricle	4
patent ductus arteriosus	5–7
patent ductus arteriosus and coarctation of aorta	8
aortic stenosis	9
aortic stenosis and coarctation of aorta	10–11
Congenital mitral insufficiency	
"Ebstein's malformation" of the mitral valve	12
Cleft septal leaflet of mitral valve associated with a left ventricular-right atrial communication and aortic obstruction	13
Fibroelastosis of mitral valve associated with patency of the ductus arteriosus	14
Atresia of the mitral valve with small foramen ovale	15–17
Unilateral congenital pulmonary venous obstruction	18

The veins were thick-walled in every case except one. It is worthy of note that the thickening of the veins even in the youngest patient was sufficiently definite to be noted at the time of the first microscopic study, which was made before the diagnosis was known to the examiner. In 9 patients intimal thickening of the veins was noted, but in only 1 patient were these changes marked. A subintimal increase in smooth muscle and elastic fibrils accounted for the major portion of the thickening.

The alteration of the structure of the alveolar wall represents the key differential finding that distinguishes the lungs of patients with pulmonary venous obstruction from those of patients with other malformations of the heart. The capillaries and their supporting structure were both affected, but the extent of involvement was variable. A progression of changes was apparent.

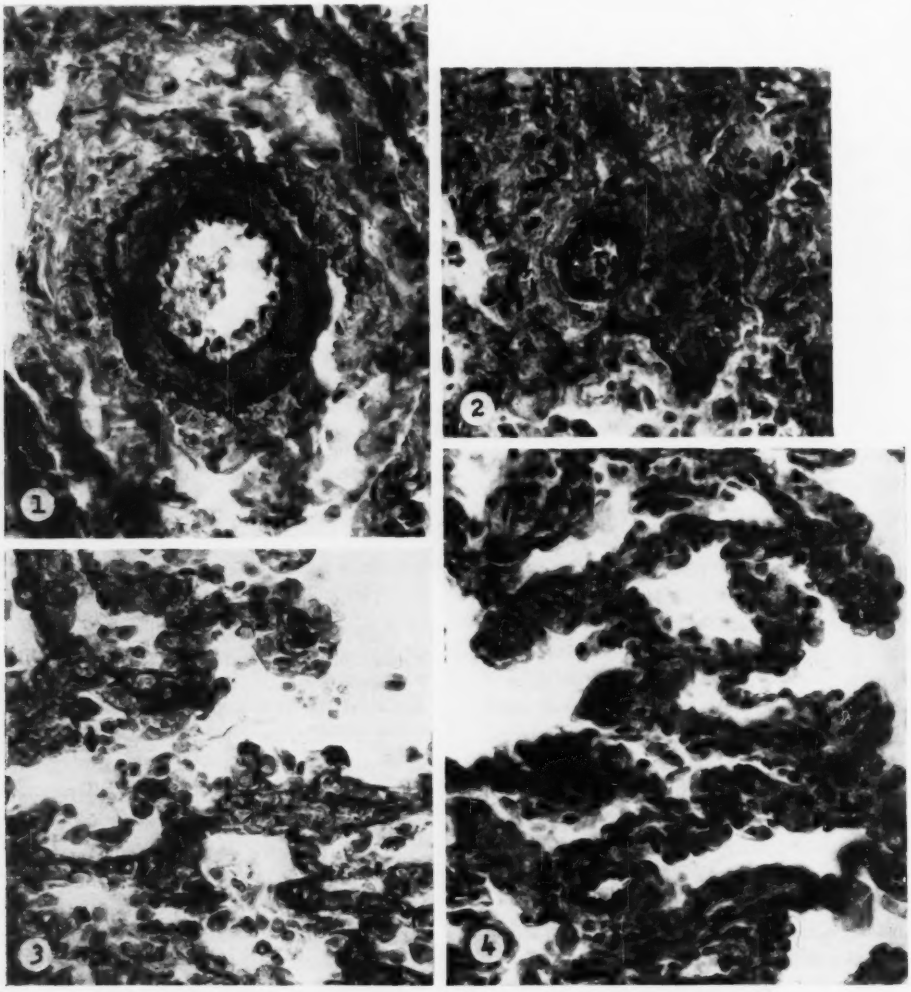

FIG. 1. Small muscular intrapulmonary artery from a 1-year-old girl with pure congenital mitral stenosis (case 2). Note medial hypertrophy and increase in elastic tissue. Elastic tissue stain. × 400.

FIG. 2. Arteriole from case 2 showing concentric cellular proliferation with marked reduction of lumen. Note also the thickened alveoli and evidence of heart failure. Elastic tissue stain. × 400.

FIG. 3. Lung parenchyma from a 26-month-old boy with congenital mitral stenosis and patent ductus (case 5) who died in pulmonary edema. Note congestion and dilatation of capillaries. Elastic tissue stain. × 400.

FIG. 4. Lung parenchyma from a 26-month-old girl with mitral insufficiency (case 13) in whom chronic left heart failure was evident from birth. Note marked cellular proliferation of alveolar epithelium. Capillaries are compressed and inconspicuous. Elastic tissue stain. × 400.

In patients with a recent history of pulmonary edema, the capillaries were dilated, tortuous, congested with blood, and were sometimes seen projecting into the alveolar spaces. The capillary basement membrane was prominent (fig. 3). Areas of capillary rupture and hemorrhage were present. The alveolar walls were thickened. In the early stages this thickening was the result of interstitial edema and deposition of a hyaline material.

A more advanced pattern was seen in patients with chronic heart failure. Interstitial collagen deposition or a proliferation of alveolar epithelial cells accounted for marked thickening of the alveolar walls. In some areas several rows of closely packed cuboidal cells interspaced with collagen material formed the alveolar walls (fig. 4). The capillaries often appeared compressed and reduced in number. The cellular appearance of the lung parenchyma was present in some of the youngest infants and was most pronounced in 2 patients with mitral regurgitation, 6 and 26 months of age, respectively. The changes were usually uniform throughout the lung parenchyma but occasionally scattered patches in different stages of progression occurred in the same lung. In a few patients advanced changes were found in the more dependent portions of the lungs, whereas early congestive changes were present in the upper lobes. Congestive cardiac failure with edema, hemorrhage and iron-laden macrophages (heart failure cells) in the alveoli occurred to a variable degree in all patients.

Additional alterations were noted in the lungs of case 18 that differed significantly from those of the other 17 patients. In this patient the pulmonary vein that drained the left upper lobe was markedly constricted and that of the left lower lobe was completely atretic. The right pulmonary veins were normal. Despite this difference the microscopic appearance of the 2 lungs was so similar that one could not distinguish the "obstructed" left lung from the "unobstructed" right lung. Marked medial hypertrophy and increase in elastic tissue, as seen in the other 17 patients, was also present in this instance, but in many vessels the media was destroyed and replaced by extensive intimal proliferation (fig. 5). In some areas this fibrous thickening resulted in complete, or nearly complete obliteration of the arterial lumen. These intimal changes occurred extensively, but not uniformly, in all areas and affected the larger as well as the small branches of the pulmonary arterial tree. The veins were thickened owing to subintimal fibrosis (fig. 6), and extreme intimal proliferation was often but not uniformly present. The changes in the lung parenchyma were similar to those of the other cases but both lungs showed areas in various stages of progression. More extensive areas of capillary dilatation and congestion with intra-alveolar hemorrhage were present in the right lung than in the left. In some portions of the lungs there was marked proliferation of alveolar epithelium with compression of the capillaries. Compensatory emphysema with thin alveolar walls was present in scattered

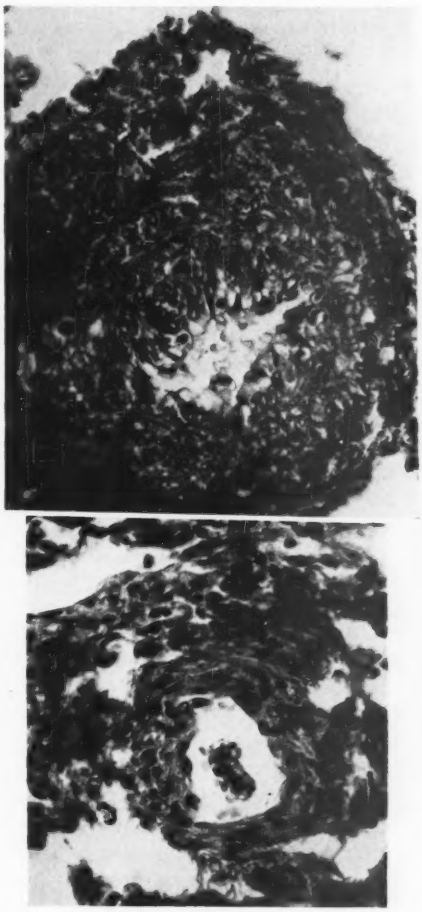

FIG. 5 *Top*. Small intrapulmonary artery from lower lobe of left lung of case 18. Note extreme intimal proliferation and destruction of the media. Elastic tissue stain. × 400.

FIG. 6 *Bottom*. Small pulmonary vein from case 18 showing thickened wall. Note also the increased cellularity of the lung parenchyma. Elastic tissue stain. × 400.

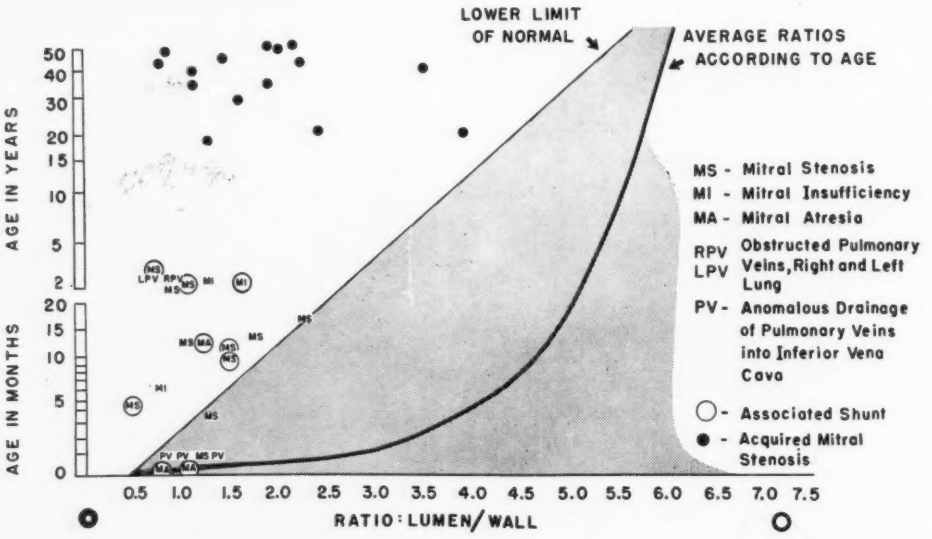
LOWER LIMIT OF NORMAL
AVERAGE RATIOS ACCORDING TO AGE
AGE IN YEARS
AGE IN MONTHS
RATIO: LUMEN/WALL
MS - Mitral Stenosis
MI - Mitral Insufficiency
MA - Mitral Atresia
RPV LPV Obstructed Pulmonary Veins, Right and Left Lung
PV - Anomalous Drainage of Pulmonary Veins into Inferior Vena Cava
- Associated Shunt
- Acquired Mitral Stenosis

FIG. 7. Ratios of pulmonary arterial lumen:wall in 18 children with congenital lesions and in 15 adults with acquired mitral stenosis.

patches in both lungs. The great variation of the alveolar changes in this patient probably depended upon the degree of obstruction of the vessel supplying or draining the affected area, but there was no clear-cut correlation.

The arterial lumen:wall ratios obtained in these patients as well as the ratios for 15 adults with acquired mitral stenosis, whose lungs were studied for comparison, are plotted in figure 7. The 18 children varied in age from birth to 3 years. The deviation from the normal in the lumen:wall ratio was more pronounced than that observed in any other group with congenital heart disease. Only the 3 youngest infants, who were under 1 month of age, showed a lumen:wall ratio within the normal range. At this age the small pulmonary arteries normally show a thick media. All other patients showed reduced ratios. The deviation from the normal in the lumen:wall ratio varied directly with the age of the patient, indicating a rapid rate of progression of the pulmonary lesions. Death occurred early. The extremely low ratios found in these children under 3 years of age were approximated only by a few of the adult patients who had had mitral stenosis for many years.

The data in figure 7 suggest that "back pressure" on the lungs during fetal life interferes seriously with the normal evolution of the pulmonary vascular bed. Narrowing of the vessels progresses rapidly and is more pronounced than that produced either by a common systolic ejectile force present from birth[9] or by long-standing acquired venous obstruction of a previously normal pulmonary vascular bed.

Pulmonary venous obstruction is present in fetal life in instances where the pulmonary veins join into a common trunk that descends into the abdomen and drains into the inferior vena cava through one of its tributaries.[12] This malformation is characterized by difficulty in emptying the pulmonary veins, a high pulmonary vascular resistance, and right-sided cardiac failure. Death usually occurs within the first month of life. A microscopic study of the lungs of 3 such patients was made for comparison. As in the other infants under 1 month of age, the lumen:wall ratios of these patients were not outside the normal range. All 3 children, however, were found to have thickened cellular alveoli and marked capillary dilatation (fig. 8) similar to the parenchymal changes noted in the other 18 patients under discussion.

Many similarities and some significant differences are revealed by a comparison of the

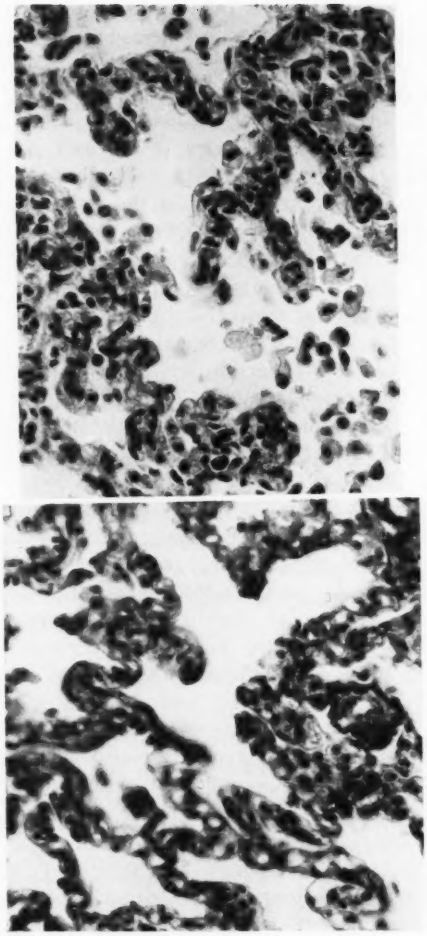

FIG. 8 *Top*. Lung parenchyma from a 21-day-old boy with anomalous drainage of pulmonary veins into a common trunk that entered the ductus venosus. Note increased cellularity of alveolar walls and dilated, congested capillaries. Elastic tissue stain. × 400.

FIG. 9 *Bottom*. Lung parenchyma from a 29-year-old man with acquired mitral stenosis. Note dilated tortuous capillaries with thickened basement membrane and increased cellularity of alveolar walls. Elastic tissue stain. × 400.

microscopic findings in the lungs of the patients in this series with those of adults with a long-standing mitral stenosis. Despite the youth of the patients with congenital malformations, the lung changes were extensive and severe. Not a single child escaped some alteration either in the pulmonary parenchyma or in the vascular tree. In contrast, only mild abnormalities were noted in several patients in the adult group. Intimal fibrosis or the deposition of a hyaline material on the endothelium was frequently found in the smaller muscular arteries in the oldest patients. Such changes may be present normally after the third decade of life.[13, 14] In every patient with acquired mitral stenosis endothelial thickening and medial hypertrophy led to a significant reduction in lumen:wall ratio. The outstanding difference between the vascular changes noted in patients with congenital obstruction of the pulmonary venous return and those with acquired mitral stenosis was the relative thickening of the media as compared to the degree of intimal change. Medial thickening was predominant in the congenital group, whereas intimal sclerosis was predominant in the acquired group. Thickening of the alveoli with dilatation and increased tortuosity of the capillaries and proliferation of the alveolar epithelial cells occurred to a varying extent in the adult patients (fig. 9), but was never so severe as in the cases with congenital heart disease. None of the adults showed the extensive cellular proliferation of the alveolar walls or the severe capillary congestion that occurred in some of the small children. In making this comparison it must be remembered that sections of the adult lungs were biopsies taken at the time of mitral commissurotomy, whereas the lung material of the pediatric age group was obtained at autopsy.

DISCUSSION

The clinical and pathologic findings in patients with congenital lesions of the left side of the heart associated with obstruction of the pulmonary venous return reveal evidence of severe and rapidly progressive pulmonary vascular and parenchymal changes. The nature of the cardiac abnormality is such that the lungs are affected prior to birth. Obstruction or insufficiency of the mitral valve leads to a rise in left atrial pressure, a consequent decrease in right-to-left shunt through the foramen ovale,[15] and an increase in right ventricular output and in the shunt from right-to-left through the patent ductus arteriosus. This increase is re-

sponsible for the large right side and the small left side of the heart at birth as well as for the thickened cellular alveolar walls that were noted in the 2 newborn infants in this series. Following birth, the increased pulmonary blood flow accentuates the alterations. The stress placed on the lungs during fetal life constitutes the major difference between these lesions and other congenital abnormalities of the heart. As a consequence, it is in this group that the most severe alterations of the lungs are noted. The shift from intra-to-extrauterine life is made more difficult by the dependence of the newborn infant upon an already embarrassed respiratory system. The 1 patient in this series whose abnormality did not place stress on the lungs during fetal life was the child with unilateral pulmonary venous obstruction (case 18). In this patient the pulmonary vascular changes were those of injury, that is, extensive intimal proliferation. This occurrence may be explained in part by the fact that the right lung with its unimpaired pulmonary venous drainage sufficed to carry the normal fetal pulmonary blood flow. Stress was placed upon the lungs after birth. The increased pulmonary blood flow exceeded the capacity of the "unobstructed" right lung and a high pulmonary pressure resulted. The left lung was exposed to the same high pulmonary arterial pressure in face of added pulmonary venous obstruction. The arterial changes in this patient suggest a state of "malignant hypertension" in the pulmonary circulation. The close similarity of the changes in the 2 lungs has not been completely explained.

The changes in the lungs resulting from "back pressure" follow a characteristic sequence, which varies in rapidity and severity. The initial changes consist of dilatation, tortuosity, and engorgement of the pulmonary veins and capillaries. Reserve vascular channels are opened. Congestion and elevated intracapillary pressure lead initially to interstitial edema, which later progresses to frank pulmonary edema. Death may occur. If congestive changes are less acute, the interstitial edema is replaced by a hyaline material and then by collagen. Alveolar cells proliferate and become cuboidal and closely spaced. The extracapillary pressure is thereby elevated and may account for the compressed capillaries noted in the most cellular areas. Such an increase in extracapillary pressure means that a higher intra-arterial pressure is required to maintain an effective flow. A vicious cycle is thereby established.

A further result of the increased pulmonary venous pressure is injury to the wall of pulmonary veins, manifested by intimal proliferation and the appearance of the elastic fibrils in the subintimal layer. Venous intimal thickening was a prominent feature in this series. Injury to the veins was more apparent than injury to the arteries. This dissimilarity was not noted in patients with acquired mitral stenosis, and may be explained by the difference between the fetal arterial bed and that of the adult. In the former, the small arteries are composed of a thick medial layer of smooth muscle and elastic fibers and a thick fibrous adventitia that offers an effective barrier to excessive stretch. In contrast, the thin-walled small pulmonary arteries of adults cannot withstand the high intravascular pressure, and injury results.

A reduction in the lumen:wall ratio was noted both in the patients with congenital heart disease and those with acquired mitral stenosis. The cause of the reduction differed. In the former group, excessive medial hypertrophy was predominantly responsible, whereas intimal change accounted for most of the thickening in the older patients.

The pathologic alterations bring about a significant reduction in the ventilatory efficiency of the lungs.[2, 16, 17] Adequate oxygenation is in part dependent upon the intimate contact of red blood cells with the pulmonary capillary wall and the proximity of the capillary wall to the alveolar space. Dilatation of capillaries, the presence of edema fluid, hyaline material, or collagen in the alveolar walls, and also edema fluid within the alveoli, all effectively slow the gaseous exchange. Alveolar thickening decreases the elasticity of the lung and thereby reduces the vital capacity. All of these combined changes bring about a pulmonary vascular resistance of great magnitude that may lead to right ventricular failure. If a large defect between the ventricles or great vessels is present, a right-to-left shunt appears and the effective pulmonary blood flow is reduced. Under these circumstances cyanosis may be present at a very early age, even from

birth. Thus the natural course of malformations of the heart in which a common ejectile force is present is accelerated by the presence of an excessive pulmonary vascular resistance caused by pulmonary venous obstruction. [18]

In the patients with congenital obstruction of the pulmonary venous return the anatomic and physiologic alterations originate in fetal life. A vicious cycle is probably initiated at birth by the sudden increase in pulmonary blood flow. The life span, however, was variable and the mode of death was not always the same. Some children died in the course of an episode of acute pulmonary edema. In these, pulmonary capillary congestion and vascular dilatation was marked. Others suffered from prolonged congestive failure. In these, cellular proliferation of the alveolar walls was a prominent feature. In 1 instance death was due to an attack of paroxysmal dyspnea that was precipitated by the severe reduction of the pulmonary blood flow. All 18 patients died before 3 years of age.

Summary

Analysis of the pathologic findings in the lungs of 18 patients with congenital lesions of the heart that caused obstruction of the pulmonary venous drainage permits the following conclusions.

When malformations of the heart are associated with pulmonary venous obstruction, severe and rapidly progressive anatomic and physiologic changes occur in the pulmonary vascular bed and in the lung parenchyma. In such instances stress upon the lungs is present prior to birth and major anatomic alterations may be found immediately after birth.

The abrupt increase in the pulmonary circulation at birth accentuates the pulmonary venous obstruction. A rapidly progressive sequence of pulmonary vascular and parenchymal changes is thereby initiated.

Arterial changes are similar to, but usually more severe than, those observed in patients who had a common systolic ejectile force. Medial hypertrophy and increase in elastic tissue are the predominant features.

Capillary, venous, and parenchymal changes are present that are not associated with other malformations except in the presence of left heart failure. Capillaries and veins show dilatation, tortuosity, and engorgement, and there is intimal proliferation of the veins. Parenchymal changes consist of interstitial edema, which is followed by collagen deposition and cellular proliferation with consequent increase in the thickness of the alveolar walls. The combination of vascular and parenchymal changes reduces the efficiency of gaseous exchange within the lungs.

The reduction in the lumen:wall ratios of the small muscular pulmonary arteries was greater than in any other group of congenital malformations of the heart. This finding suggests that pulmonary venous obstruction is an important factor in the pathogenesis of pulmonary arterial narrowing.

A comparison of these findings in young individuals and in adults with acquired mitral stenosis shows that changes are more extreme and more rapidly progressive in the congenital than in the acquired forms of pulmonary venous obstruction.

Summario in Interlingua

Le analyse del constatationes pathologic in le pulmones de 18 patientes con congenite lesiones del corde que causava obstruction del drainage pulmono-venose permitte le sequente conclusiones:

Quando malformationes del corde es associate con obstruction pulmono-venose, sever e rapidemente progressive alterationes anatomic e physiologic occurre in le vasculatura pulmonar e in le parenchyma del pulmon. In tal casos, stress affice le pulmones ante nato, e major alterationes anatomic pote esser trovate immediatemente post le nascentia.

Le abrupte augmento del circulation pulmonar al tempore del nascentia accentua le obstruction pulmono-venose. Un rapidemente progressive sequentia de vascular e parenchymal alterationes pulmonar es assi initiate.

Le alterationes arterial es simile a illos observate in patientes con un commun fortia ejectile systolic. Usualmente illos es plus sever. Hypertrophia medial e augmento de tessuto elastic es le characteristicas predominante.

Alterationes capillar, venose, e parenchymal es presente que non es associate con altere

malformationes excepte in le presentia de disfallimento sinistro-cardiac. Capillares e venas exhibi dilatation, tortuositate, e retention, e il ha proliferation intimal del venas. Le alterationes parenchymal consiste de edema interstitial, sequite per deposition de collageno e proliferation cellular e consequente augmentos del spissitate del parietes alveolar. Le combination del alterationes vascular e parenchymal reduce le efficacia del excambio gasose in le pulmones.

Le reduction del proportion passage: pariete in le parve arterias pulmonar muscular esseva plus grande que in non importa qual altere gruppo de malformationes congenite del corde. Iste constatation suggere que obstruction pulmono-venose es un factor importante in le pathogenese del restriction pulmono-arterial.

Un comparation de iste constatationes in juvene individuos e in adultos con acquirite stenosis mitral revela que le alterationes es plus extreme e plus rapidemente progressive in le forma congenite que in le forma acquirite de obstruction pulmono-venose.

Acknowledgment

We express our gratitude to Dr. F. W. Wiglesworth, Pathologist, Montreal Children's Hospital, Montreal, Canada, Dr. G. J. Hummer, Pathologist, St. John's Hospital, Santa Monica, California, and Dr. David Smith, Pathologist, University of Virginia Hospital, Charlottesville, Virginia, for their continued support of this work. We wish to thank Dr. Helen B. Taussig for her advice and many helpful suggestions.

Appendix

*Synopses of clinical and anatomic findings**

Case 1. L. D. (C.M.H. Autopsy #A51-117) 3¾ months. Rapid respirations. No murmur. Electrocardiogram: right ventricular hypertrophy. X-ray: slight cardiac enlargement, pulmonary congestion. Anatomic diagnosis: Double left atrium: pulmonary veins emptying into upper chamber with 3-mm. orifice opening into lower chamber. Lumen:wall ratio 1.30.

Case 2. C. C. (J.H.H. Autopsy #25527) 1 year. Sudden congestive heart failure at 7 months. Systolic murmur and loud diastolic rumble at apex, loud first and second heart sounds. Electrocardiogram: marked right ventricular hypertrophy, notched P waves. X-ray: marked cardiac enlargement, large left atrium, pulmonary congestion. Cardiac catheterization: pulmonary artery pressure 54/17 mm. Hg. Angiocardiogram: Large left atrium with delayed emptying. Died following mitral valvotomy. Anatomic diagnosis: Severe mitral stenosis. Lumen: wall ratio 1.10.

Case 3. C. R. (C.M.H. Autopsy #49-36) 10½ months. Cyanotic from birth. No murmur. Electrocardiogram: marked right ventricular hypertrophy. Died of paroxysmal dyspnea. Anatomic diagnosis: Marked mitral stenosis. High ventricular septal defect with slight overriding of the aorta. Lumen:wall ratio 1.41.

Case 4. F. K. (J.H.H. Autopsy #21539) 3 years. Dyspnea since infancy. Cyanosis after 18 months of age. Loud systolic murmur. Loud pulmonic second sound. Electrocardiogram: combined ventricular hypertrophy. X-ray: no cardiac enlargement. Heavy hilar vascular markings. Died of pneumonia and congestive heart failure. Anatomic diagnosis: Single ventricle with transposition of the great vessels, stenotic mitral valve, patent foramen ovale. Lumen: wall ratio 0.71.

Case 5. J. H. (C.M.H. Autopsy #52-147) 26 months. Attacks of orthopnea after 1 year of age. Terminal severe congestive failure. Recurrent cyanosis of left hand and feet. Systolic and inconstant diastolic murmur at apex. Electrocardiogram: right ventricular hypertrophy. Cardiac catheterization: systemic pressure in pulmonary artery. Died following surgery. Anatomic diagnosis: Mitral stenosis and patent ductus arteriosus, ligated. Lumen:wall ratio 0.96.

Case 6. E. R. (J.H.H. Autopsy #22949) 1 year. Cyanosis of left hand and feet since 3 days of age. Loud pulmonary systolic murmur. Electrocardiogram: right ventricular hypertrophy. X-ray: no cardiac enlargement, increased hilar vascular markings. Angiocardiogram: filling of descending aorta from pulmonary artery. Died following surgery. Anatomic diagnosis: Mitral stenosis and patent ductus arteriosus, ligated. Lumen:wall ratio 1.41.

Case 7. R. C. (C.M.H. Autopsy #54-93) 4½ months. Occasional cyanosis of left hand and feet. Sudden onset of pulmonary edema at 3 months. Loud systolic murmur, diastolic murmur in fourth left intercostal space. Angiocardiogram: large left atrium and left ventricle. Died following mitral

* The patients were studied at the following hospitals: The Johns Hopkins Hospital, (J. H. H.), Baltimore, Maryland, The University Hospital (U. V. H.), Charlottesville, Virginia, The Children's Memorial Hospital (C. M. H.), Montreal, P. Q. Canada, and St. John's Hospital (S. J. H.), Santa Monica, California.

Cases 3, 5, 8, 9, 10 and 11 have previously been reported.[18] Reports on case 12 and on case 13[19] are in preparation.

valvotomy. Anatomic diagnosis: Mitral stenosis and patent ductus arteriosus. Lumen:wall ratio 0.47.

Case 8. A. C. (C.M.H. Autopsy #39-57) 13 months. Difficult respirations. Large heart. Systolic murmur at base transmitted to the neck. Anatomic diagnosis: Mitral stenosis, aortic stenosis, mild coarctation of the aorta and patent ductus arteriosus distal to site of coarctation. Lumen:wall ratio 1.77.

Case 9. H. B. (C.M.H. Autopsy #52-117) 16 months. Attacks of "asthma" since early infancy. Enlarged heart, soft systolic murmur at apex. Died of paroxysmal dyspnea. Anatomic diagnosis: Mitral stenosis and aortic stenosis. Lumen:wall ratio 2.3.

Case 10. D. O. (C.M.H. Autopsy #A51-66) 3 weeks. Severe congestive heart failure. Loud systolic murmur at base. Electrocardiogram: normal. Anatomic diagnosis: Mitral stenosis, aortic stenosis, mild coarctation of aorta, patent ductus arteriosus. Lumen:wall ratio 1.2.

Case 11. D. G. (C.M.H. Autopsy #A51-80) 25 months. Sudden respiratory distress at 8 months of age. Congestive heart failure. Absent femoral pulses. Systolic murmur at lower left sternal border. Electrocardiogram: right ventricular hypertrophy. Angiocardiogram: large left atrium with delayed emptying. Died at operation. Anatomic diagnosis: Mitral stenosis, subaortic stenosis, and coarctation of the aorta. Lumen:wall ratio 0.94.

Case 12. R. J. (S.J.H. Autopsy #A10-54) 6 months. Minimal cyanosis since birth. Cardiac failure at 10 weeks. Loud mitral first sound and split second sound. Short systolic murmur and diastolic rumble at apex. Electrocardiogram: right ventricular strain. X-ray: marked enlargement of right ventricle and left atrium. Cardiac catheterization: systemic right ventricular pressure. Died following catheterization. Anatomic diagnosis: Downward displacement of the mitral valve, posterior leaflet originated from left ventricular endocardium with a large portion of left ventricle incorporated into the left atrium ("Ebstein's malformation" of the mitral valve.) Functional stenosis and insufficiency of mitral valve. Lumen:wall ratio 0.80.

Case 13. M. T. (J.H.H. Autopsy #26103) 26 months. Neonatal congestive heart failure improved with digitalis. Loud systolic and diastolic murmurs. Electrocardiogram: marked left ventricular hypertrophy. Notched P waves. X-ray: large left atrium, diffusely increased hilar markings. Cardiac catheterization: pulmonary artery wedge pressure 18 mm. Hg, pulmonary artery pressure 43/35 mm. Hg. Died during operation. Anatomic diagnosis: Mitral insufficiency due to cleft septal leaflet of mitral valve. Left ventricular-right atrial communication, partially occluded by fibrous network that obstructed the aortic outflow tract. Lumen:wall ratio 1.30.

Case 14. E. W. (J.H.H. Autopsy #22443) 25 months. Congestive cardiac failure at 6 months of age, improved with digitalis. Systolic and diastolic murmurs at apex. Electrocardiogram: right ventricular hypertrophy. X-ray: heart large. Cardiac catheterization: large left-to-right shunt, pulmonary artery pressure 70/56. Died following ligation of large patent ductus. Anatomic diagnosis: Mitral insufficiency due to thickening and deformity of valve leaflets and chordae tendineae. Patent ductus arteriosus. Lumen:wall ratio 1.64.

Case 15. D. L. (C.M.H. Autopsy #A46-48) 1 year. Cyanotic since birth. No cardiac enlargement. To-and-fro murmur heard occasionally. Anatomic diagnosis: Mitral atresia, patent foramen ovale, ventricular septal defect, coarctation of the aorta, patent ductus arteriosus distal to site of coarctation. Lumen:wall ratio 1.15.

Case 16. B. B. (S.J.H. Autopsy #A17-1-54) 4 hours. Intensely cyanotic. No murmur. Anatomic diagnosis: Mitral atresia. Aortic atresia. Patent ductus arteriosus. Lumen:wall ratio 1.03.

Case 17. V. L. M. (S.J.H. Autopsy #A6-4-52) 4 days. Severe cyanosis. Right heart failure. Faint basal systolic murmur. Electrocardiogram: marked right ventricular hypertrophy. X-ray clear lungs, enlargement of right atrium and right ventricle. Died during surgery. Anatomic diagnosis: Mitral atresia. Aortic atresia. Small foramen ovale. Dilated right ventricle and pulmonary artery. Rudimentary left ventricle. Lumen:wall ratio 0.75.

Case 18. H. R. D. (U.V.H. Autopsy #6385) 2½ years. Sudden onset of severe recurrent hemoptysis at 1½ years, followed by progressive dyspnea, and orthopnea. Gallop rhythm. Loud, split pulmonic second sound. Decrescendo diastolic murmur. Right heart failure. Electrocardiogram: marked right ventricular hypertrophy. X-ray: clouding of the left lung, large heart, prominent pulmonary artery. Cardiac catheterization: pulmonary artery pressure 80/40 mm. Hg. Died suddenly. Anatomic diagnosis: Atresia of left lower lobe pulmonary vein. Severe constriction of left upper lobe pulmonary vein. Right pulmonary veins normal. No cardiac defect. Lumen: wall ratio right lung 0.88, left lung 0.70.

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Ebstein's Anomaly

Presentation of Ten Cases

By Florence E. Mayer, M.D., Alexander S. Nadas, M.D., and Patrick A. Ongley

Ten cases of Ebstein's anomaly are presented and the literature is reviewed. Certain diagnostic features of the clinical profile, in particular the auscultatory findings, are emphasized.

SINCE first described by Ebstein in 1866,[1] approximately 80 cases of this anomaly have been reported.[2-49] Its differentiation from forms of congenital heart disease amenable to surgery is of importance and in the majority of cases may be accomplished by clinical means.

The 10 cases studied at the Children's Medical Center, Boston, ranged in age up to 25 years. There were 4 males and 6 females. Postmortem material was available in 4, cardiac catheterization had been performed in 4, and angiocardiography in 2. One cardiac catheterization was performed at the Maine General Hospital, Portland, Me.

Results

History and Physical Examination

Symptomatology was evaluated in 9 patients. Slightly increased fatigability and mild dyspnea on exertion were present in all patients over 1 year of age. Severe dyspnea occurred only with the onset of congestive failure. Cyanosis was observed in the neonatal period in 6 cases; 2 of these subsequently became cyanotic only with crying or activity. Cyanosis appeared after infancy in 2, and 1 patient at the age of 25 years had never been cyanotic. Three patients developed congestive failure in the neonatal period, at 2 years, and at 8 years of age, respectively. Paroxysmal atrial tachycardia occurred in 1 case. Squatting was observed infrequently in 2 patients and in only 1 was an anoxic spell with loss of consciousness described.

Examination of these patients revealed normal growth in the majority. Five were mildly cyanotic but only 2 presented clubbing. The cardiac impulse was not forceful and extended diffusely from sternum to apex. A systolic thrill was palpable between xiphoid and apex in 6 patients. On auscultation the outstanding findings, noted in 8, were a triple or quadruple rhythm, a diminished pulmonary second sound, and systolic and diastolic murmurs of medium frequency, heard maximally at the lower left sternal border and apex. The systolic murmur was frequently described as "scratchy" or coarse.

Phonocardiogram

Sound tracings available on 5 patients showed remarkable similarity (fig. 1). The first heart sound was delayed and normal in intensity, maximal at the apex. The second heart sound was maximal at either the lower left sternal border or apex in all cases, and was narrow or unsplit in 3. All presented a third sound, and in 3 a fourth sound was observed as well.

A systolic murmur of moderate intensity and of medium frequency and decrescendo or crescendo-decrescendo in configuration was recorded in all tracings. Also uniformly recorded was a presystolic murmur of medium frequency and intensity. A very low frequency mid-diastolic murmur was present in 2. These murmurs were of greatest intensity at the left lower sternal border or apex.

Electrocardiogram

Electrocardiographic studies were done in 9 cases. Tall, peaked or broad P waves over 2.5 mm. in leads II, V_1, and V_2 were present in 8 patients and in many they measured over 4 mm. in height. Atrioventricular conduction was prolonged in 5 tracings.

Right bundle-branch block was a constant finding: in 4 the QRS complex measured 0.12

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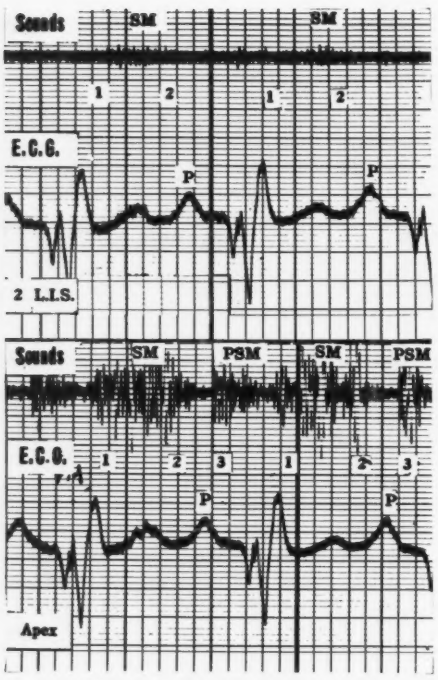

FIG. 1. Phonocardiogram of patient L.H., age 2 years. The first sound, *1*, of normal intensity is best recorded at the apex; it occurs 0.10 second after the q wave. The second sound, *2*, is of normal intensity, maximal at the apex and split 0.04 second wide, with the first component louder than the second. A loud diastolic sound, *3*, may be a summation sound. Crescendo-decrescendo systolic murmur *SM* is of medium frequency and maximal at the apex. Late diastolic presystolic murmur *PSM* of moderate intensity is decrescendo in configuration and maximal at the apex. *2 LIS* = second left interspace.

second or more; in the remainder the block was incomplete. Ventricular potentials of small amplitude in the right precordial leads were observed in all who were beyond early infancy. Paroxysmal atrial tachycardia was documented by electrocardiogram in 1 patient; frequent ventricular ectopic beats were seen in another.

The evolution of the characteristic electrocardiographic pattern is observed in figure 2. The first electrocardiogram taken at 3 days of age showed complete reversal of the adult R/S progression from V_4R to V_6 with an R in V_1 of 20 mm. It was within normal limits for age. In the second tracings at 3½ years of age there had appeared prolonged atrioventricular conduction with a P-R interval of 0.20 at a rate of 105 per minute, P-pulmonale with a P in lead II of 5 mm., incomplete right bundle-branch block, and potentials of low amplitude in the right precordial leads.

Radiologic Examination

Marked cardiomegaly involving the right side of the heart was noted by roentgenologic examination in all patients (fig. 3). The contour was frequently described as "globular." A narrow base with a small aorta was typical; the pulmonary artery was poorly visualized in 7 patients and the pulmonary vascular markings were decreased in all except 1. Diminution in the amplitude of cardiac pulsation was specifically noted in 3 cases.

Angiocardiography

Two patients were studied by angiocardiography (figs. 4 and 5). The dye entered a huge atrial chamber where it was greatly diluted and from which it emptied slowly. In one patient the pulmonary artery filled poorly; in the other it appeared normal. A right-to-left shunt was suggested by simultaneous opacification of the aorta and pulmonary artery in both cases; in one the shunt was demonstrated at the atrial level.

Figure 5 was taken in a child who had been in chronic congestive failure and who died shortly after the procedure. He was found at postmortem examination to have a markedly dilated distal as well as proximal right ventricular chamber.

Cardiac Catheterization

This procedure was performed in 4 patients; it was not completely satisfactory in any instance, but yielded suggestive information in 3 (table 1). In each the catheter coiled in a large atrium (fig. 6). In patient S. P. a predominant "a" wave with a peak of 2.5 to 5 mm. Hg was obtained in this chamber. The pulmonary artery could not be entered; the right ventricular systolic pressure was within normal limits. Unsaturation of left atrial blood suggested a right-to-left shunt at this level. Peripheral arterial oyxgen saturation was 85 per cent.

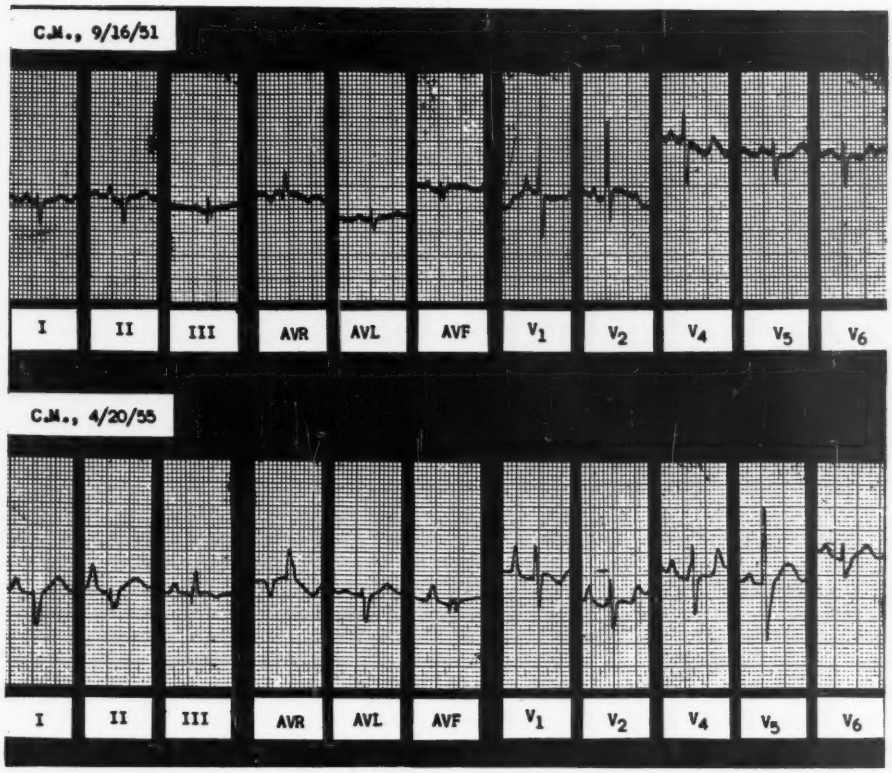

FIG. 2. Evolution of characteristic electrocardiographic pattern in patient C.M. from age 3 days (upper tracing) to age 3 years (lower tracing).

In patient R. B. it was impossible to proceed to the right ventricle because of the appearance of the ectopic beats when the tricuspid valve area was approached. This region appeared to lie farther to the left than normal. Peripheral arterial saturation was 95 per cent. A rise in oxygen saturation at the atrial level suggested a small left-to-right shunt. In patient J. L. the catheter entered an area with a right ventricular pressure curve at a "lower" site than normal. Systolic pressure in the right ventricle was not elevated and there was no gradient across the pulmonary valve. Peripheral arterial saturation was 90 per cent.

Course

Six patients are doing well and have minimal symptoms. One has had frequent episodes of paroxysmal atrial tachycardia eventually controlled with digitalis.

Four patients have died. The first, a stillborn, died presumably as a result of a prolapsed cord in a difficult breech delivery. The second child, L. C., a 9-day-old infant, died in severe congestive failure, and at postmortem examination was found to have a hypoplastic aorta and coarctation as well as Ebstein's anomaly. The third patient, L. H., was a 2-year-old boy, cyanotic since birth, who had been treated for congestive failure on admission, with good response. He developed marked bradycardia and coma during angiocardiography and died 36 hours later. The fourth patient, C. C., an 8-year-old girl, had been in congestive failure for several months and was rapidly deteriorating. She had been cyanotic since 4½ years of age. Cardiac arrest occurred during cardiac catheterization and she failed to recover.

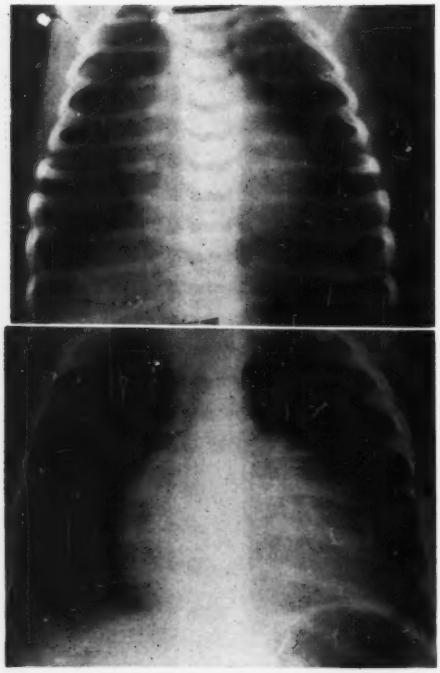

FIG. 3. Representative posteroanterior roentgenograms of patient C.M. (left) *top*, at 3 days of age and *bottom*, at 3 years of age.

FIG. 4. S.P., age 8 days. Angiocardiogram in left lateral position. The large chamber of the right atrium and proximal right ventricle was opacified from the inferior vena cava. The pulmonary artery and aorta opacified simultaneously.

Postmortem Material

Autopsies were performed in 4 cases. In each instance the weight of the heart was 2 to 3 times normal. The right atrium was markedly dilated

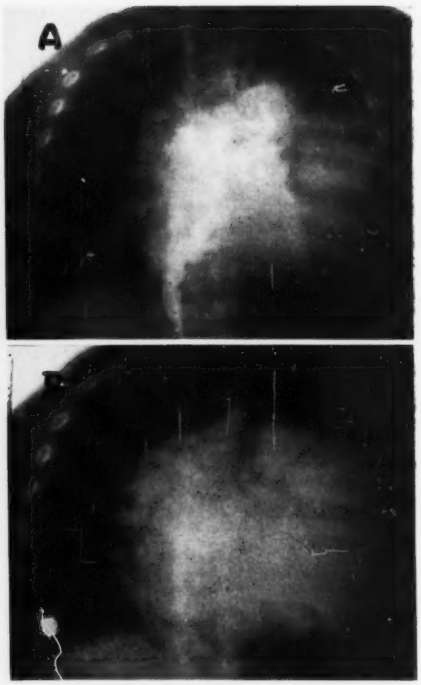

FIG. 5. L.H., age 2 years. Angiocardiogram in anteroposterior position. *A*. Dye entered a large chamber from inferior vena cava. *B*. A huge chamber representing right atrium and proximal right ventricle is outlined. The dilated distal portion of the right ventricle must also be opacified but the line of demarcation is not clear. The left atrium filled early and the aorta was seen simultaneously with the pulmonary artery.

in all, with hypertrophied muscle bundles lining the wall of the atrium and its appendage. These muscles bundles were prominent in the atrial wall of the stillborn.

The foramen ovale was patent in every case. In 1 patient a small ventricular septal defect was present as well.

The right ventricle was divided into proximal and distal portions by the misplaced valve leaflets. In the stillborn (fig. 7) these were distinctive, the proximal portion forming a thin-walled pocket measuring 1.2 cm. by 1.6 cm., the distal or outflow portion being of normal appearance and thickness. No histologic defect in the cellular structure of the proximal ventricular myocardium was observed.

In patient L. C., who had a complicated lesion, the divisions of the right ventricle were

TABLE 1.—*Findings on Cardiac Catheterization in Three Cases of Ebstein's Anomaly of the Tricuspid Valve*

Patient and age	O_2 content volume per cent						O_2 capacity	Pressure, mm. Hg			Flow/M.²	
	SVC	RA	RV	PA	LA	BA		RA*	RV	PA	Pulm.	Syst.
S. P., 8 days.....	13.5	14.7	14.7	—	19.8	18.4	21.6	M-0.5	35/2/3	—	3.5	3.5
R. B., 4 yrs.....	12.7	14.5	—	—	—	17.3	18.1	M-5	—	—	—	—
J. O., 25 yrs.....	9.8	11.3	12.1	12.5	—	16.7	20.3	M-3	13/3	12/7	1.5	1.6

* M = Mean pressure

not so well differentiated; the distal portion was somewhat dilated and hypertrophied and measured 4 mm. in thickness. The dilated proximal portion was variable in thickness, averaging 2 mm.

In patient L. H., who had been in congestive failure, both the proximal and distal divisions were dilated and thin walled and the pulmonary valve appeared thickened (fig. 8). Patient C. C., in whom congestive failure had also been present, had a paper-thin, 12 by 15 cm. proximal portion and a dilated distal division measuring 9 by 6 cm. (fig. 9). In this case the pulmonary valve appeared to be dilated.

The abnormal valve cusps varied in detail from one patient to another. In the stillborn the anterior cusp was normal in structure and in its origin from the valve ring. The posterior and medial cusps, arising 1 cm. below the ring from the wall of the right ventricle and its septum, were adherent to the wall and to sparse, thin chordae tendineae. The endocardium showed no evidence of scarring. In patient L. C., the picture was similar, with a normal anterior leaflet, and with small posterior and septal leaflets arising from the right ventricular wall midway between valve ring and apex. No chordae or papillary muscles were attached to these leaflets. In patient L. H., the anteromedial, medial, and a small part of the posterior leaflet arose from the ring; the anterolateral and most of the posterior cusps, from the wall of the right ventricle 1 to 3 cm. below the valve ring. The displaced cusps were almost completely adherent to the wall and there were no well-formed papillary muscles in this area. In patient C. C., the anterior leaflet arose as a large membranous curtain, 8 by 6 cm. in measurement, from the valve ring; the left border was attached to the ventricular wall, the right border was free. The septal leaflet was

FIG. 6. C.C., age 8 years. Roentgenogram illustrating catheter coiled in large right atrium.

normal. The posterior leaflet arose from the ventricular wall, was poorly developed, and was bound down to the wall.

In each instance, passive congestion of the liver was noted.

Patient L. C. had additional malformations of the great vessels: a hypoplastic aorta with a coarctation 1 cm. in length proximal to a patent ductus arteriosus. Patient C. C. had a probe-patent ductus arteriosus.

DISCUSSION

Clinical Findings

The symptomatology of Ebstein's anomaly is generally mild. A number of patients have been asymptomatic, in particular those who survived to an advanced age.[2, 6, 7] Cyanosis, persistent or intermittent, was observed in about four fifths of the cases; in one third it was present from birth. The most common

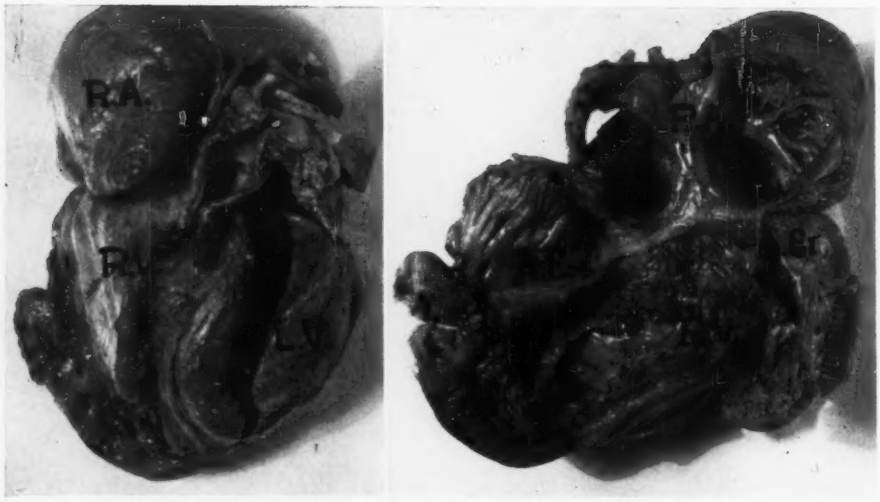

FIG. 7. *Left.* Photograph of heart of stillborn infant. *RA*, large right atrial appendage; *RV*, right ventricle; *LV*, left ventricle. *Right.* Interior of same heart. *RA*, right atrium; *FO*, foramen ovale. *AF*, annulus fibrosus; *PC*, posterior cusp of tricuspid valve taking origin 1 cm. below valve ring; *AC*, anterior cusp of tricuspid valve arising from valve ring; *RV*, distal right ventricle. Note hypertrophied muscle bundles in the atrial wall and thin-walled pocket lying between the annulus and the origin of the posterior cusp.

history was one of cyanosis appearing some time after infancy, intermittent with cold or exertion at first, and gradually becoming more marked.

Slight to moderate dyspnea and fatigability are almost invariably present, appearing usually after the period of early childhood. Cardiac arrhythmias are extremely frequent; 5 patients had documented paroxysmal atrial tachycardia,[19, 20, 27, 46] 1 had atrial fibrillation,[33] and another had atrial flutter.[44] Wolff-Parkinson-White syndrome was described in 1 case.[39] About one third of all patients experienced bouts of palpitation. Squatting, anoxic spells, and precordial pain are uncommon.

At least 12 cases have been in congestive failure. In 5 patients it occurred in the first decade, in 5 others in the second decade. Its occurrence is probably a poor prognostic sign. Only 2 were alive at the time of reporting; one was a 29-year-old man living 5 years after his first bout of failure.[32] In the remainder there were, at least as an associated cause of death, pulmonary tuberculosis in 2,[1, 9] myocardial infarction in 2,[19, 35] erysipelas in 1, embolism in 1,[5] and fatal outcome of diagnostic procedures in 2.

Almost without exception these patients were normal in growth. Clubbing of the fingers has been noted in about one third. Precordial chest deformities were infrequent and the cardiac impulse was commonly diffuse and quiet. In the majority, a systolic thrill was palpable between xiphoid and apex.

Auscultatory findings of wide variety have been described in the literature. The findings in our series have been so uniform as to be characteristic: a triple or quadruple rhythm; a second sound maximal in intensity at the lower left sternal border or apex; a medium frequency, moderate intensity systolic murmur decrescendo or crescendo-decrescendo in contour, and a late diastolic or presystolic murmur of moderate intensity, both maximal at the xiphoid or apex. These characteristic findings may not be present, however, for 6 patients,[16, 18, 27, 29, 47] including one of our own, had no murmurs at all.

It has frequently been commented that clinical signs of tricuspid insufficiency are rarely seen. A pulsating liver was noted in none of our cases and pulsating neck veins only in a patient in failure. It has been suggested that clinical signs of insufficiency may be lacking

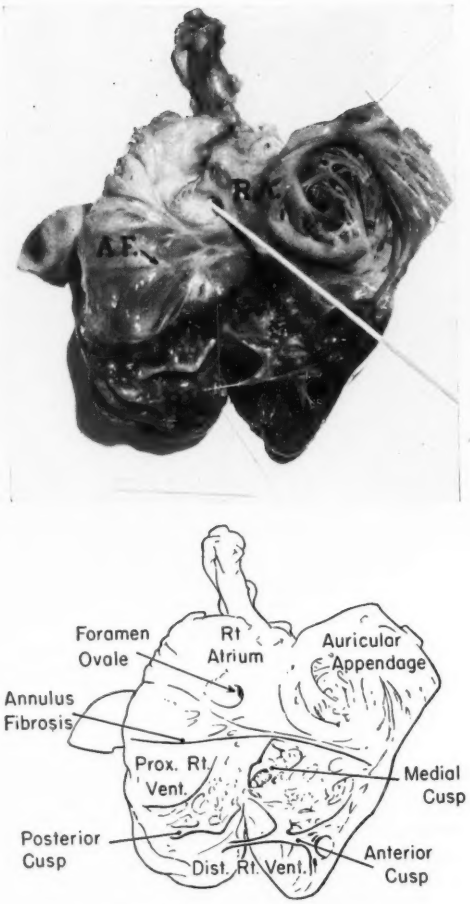

FIG. 8. L.H., age 2 years. Photograph (*top*) and diagram (*bottom*) of interior of heart. The distal division of the right ventricle in this patient who had chronic congestive failure was thin walled.

because of the great distensibility of the combined chamber above the tricuspid valve, which allows regurgitation of a considerable volume of blood without transmission of a visible pressure wave to the systemic veins.[43]

The hugely dilated and hypertrophied right atrium is reflected in the characteristic tall P waves of the electrocardiogram, which with right bundle-branch block and low amplitude of right ventricular potentials have been almost constant findings in all the cases. Prolonged atrioventricular conduction is common. The characteristic pattern may not be present in early infancy;[48] in our patient also this pattern developed over a 2-year period. Abnormally tall right ventricular potentials have been reported in 2 cases, case C of Kjellberg et al.,[43] and case III of Brown et al.,[47] so that the diagnosis of Ebstein's anomaly cannot be entirely dismissed in the presence of tall right ventricular potentials.

The radiologic picture characteristically is one of marked cardiomegaly, a contour consistent with right-sided enlargement, a narrow base, diminished pulmonary vascular markings, and a poorly delineated pulmonary artery. Fluoroscopically, pulsation of the right border is frequently weak although a few observers have described increased presystolic pulsations. The contour of the heart mimics that of pericardial effusion and the amplitude of pulsation in each instance is diminished. The similarity of the roentgenologic picture to that of severe pulmonic stenosis with intact ventricular septum has been pointed out.[21]

Angiocardiography has been performed in 23 cases. Ours appears to be the only reported fatality due to the procedure. Characteristically, the dye opacifies and is greatly diluted in a huge chamber representing right atrium and proximal right ventricle. This chamber shows delayed emptying and obscures to a large extent the remainder of the cardiac silhouette. The pulmonary artery and its branches are poorly opacified. Several authors have demonstrated a distinct small outflow portion of the right ventricle, filling later, and separate from the large chamber. Evidence of a right-to-left shunt has been observed in about one half of the cases by early opacification of the aorta or by observation of the dye shunting to the left atrium. The information obtained from the procedure does not appear to be pathognomonic and does not contribute greatly to the diagnosis.

Cardiac catheterization (table 2) has been reported in 38 patients and was performed in 4 of our own. Seven of the cases were proved by autopsy. There is a marked tendency toward the development of arrhythmias, and the procedure carries with it a definite hazard: 3 patients have died during or shortly after the procedure.[26, 29] A fourth[23] died 21 days later with emboli that produced gangrene in both lower extremities and thrombi in branches of

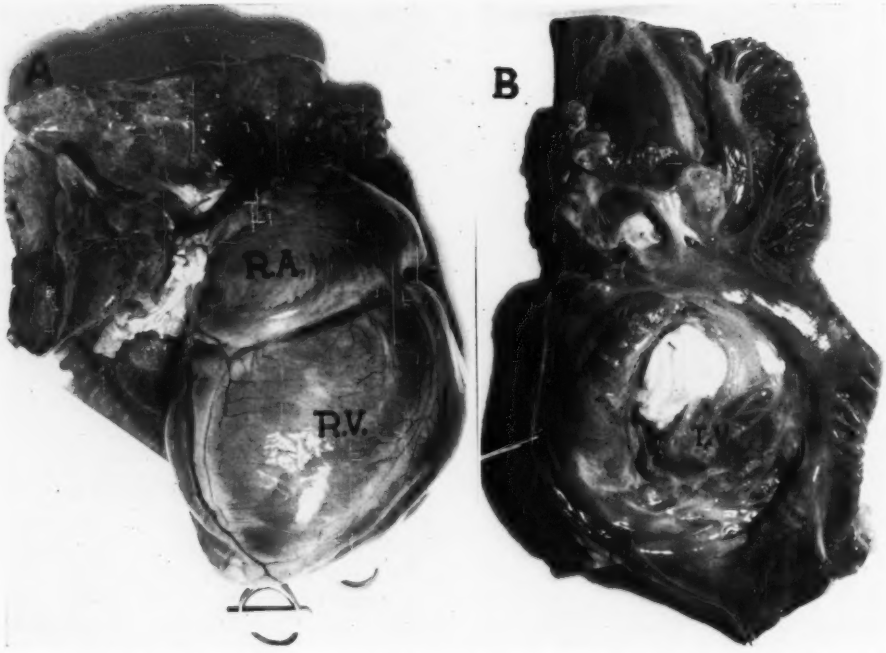

FIG. 9. C.C., age 8 years. *A*. Exterior of the heart illustrating large right atrium, *RA*. *RV*, right ventricle. *B*. Interior of same heart. The right atrium is opened and the tricuspid valve, *TV*, is viewed from above. The large membranous anterior cusp arises from the valve ring.

the left coronary artery. Thrombi were present in the left atrium and left ventricle, both of which had been explored with the catheter. In addition, Campbell[36] in an editorial states that both he and Wood have lost 1 patient in 5 or 6 who were catheterized. We think, however, that in questionable cases more pertinent information may be gained from catheterization than from angiocardiography.

The malformation results in a reduction in size of the functioning right ventricle. Pulmonary flow may be diminished, and with a rise in pressure in the atrial chamber a right-to-left shunt may occur at the atrial level.

Typically the catheter coils in the huge right atrial chamber. The tricuspid valve appears to lie to the left of its usual position and the right ventricle may be entered with difficulty. Arrhythmias frequently occur as the catheter approaches the valve area.

A number of observations may be made from the reported data. Peripheral arterial unsaturation is usual. Only 9 cases with arterial saturation over 90 per cent have been reported. Postmorten examination revealed no interatrial communication in 2 cyanotic patients, and it has been suggested that cyanosis may be of a peripheral type in some instances because of a low cardiac output.[43]

Ten cases revealed at the atrial level a rise in oxygen saturation of sufficient degree to suggest a left-to-right shunt of small magnitude. Right atrial mean pressures are usually moderately elevated. The pressure contour has been described in a number of cases: in 8 a predominant V wave was observed suggesting that tricuspid insufficiency is indeed present in many. One patient,[43] in whom a "v" wave of 14 mm. was recorded, died in congestive failure and was found to have a greatly dilated distal right ventricular chamber. In 7 cases an "a" wave was predominant. Transmission of this atrial wave to the right ventricle and pulmonary artery has been described[48] and it has been suggested that the contraction of the atrial chamber may supplement the right ventricular func-

TABLE 2.—*Summary of Catheterization Data in Thirty-Eight Reported Cases of Ebstein's Anomaly*

Author and ref. no.	Pressure in mm. Hg			Peripheral arterial O_2 saturation	Suggestive L-R shunt at atrial level	Autopsy evidence of atrial communication
	R. A.	R.V.†	P.A.			
Engle[21]	8/1	21/7	*	66	+	F.O.
Brown[46]	4		10			
Brown[46]	14					None
Brown[46]	11					
Blacket[29]	4	8 8	8			
Kjellberg[43]	v wave	14/5	13/7	81		
Kjellberg[43]	M-10 v wave 14 mm.	36/6	24/7	90		None
Kjellberg[43]	M-13 v wave 13 mm.	23/8	24/8	94		
Kjellberg[43]	M-10 v wave 15 mm.	33/9	27/17	85		
Tourniare[20]	15	15	20			
Medd[40]	8/4	18/4				
Van Lingen[30]	7/4	22/4	22/10	87	+	
Van Lingen[30]		22/8	22/10	69	+	
Gøtzsche[39]	7/2	18/2	14/8	87	+	
Gøtzsche[39]	8/2	27/2	16/4	89		
Gøtzsche[39]	8/1 v wave	25/1	*	89		
Gøtzsche[39]	15/3 v wave	22/4	17/10	93		
Gøtzsche[39]	2	15/0	15/8	96		
Gøtzsche[39]	3	24/2	16/6	90	+	
Broadbent[32]	10/4	13/4 19/4	20/10	89	+	
Broadbent[32]	11/4	11/4 18/3	18/10	62		F.O.
Broadbent[32]	25/13 v wave	34/10 33/13	34/22	84		
Kerwin[49]	16/10	32/6		86		None
Henderson[33]	7	9	14	91		
Goodwin[34]	2.5					
Grob[31]		10/0 30/0	30/15			
Baker[23]	10	*	*	75		A.S.D.
Baker[23]	not given	*	*	93		A.S.D.
Reynolds[24]	11–17	*	*	79	+	
Bayer[41]	10/0 v wave	20/0 26/0	26/10	80	+	
Bayer[41]	7/3 a wave	10/3 18/0	15/9	78	+	
Bayer[41]	4/0 a wave	7/0 15/0	15/7	79		
Schaede[26]	not given					
Schaede[26]	not given				+	F.O.
Blount[48]	7/2 a wave	24/0/4	19/9	90.9		
Blount[48]	12/5 a wave	24/4/11	20/9	76.6		
Blount[48]	10/4 a wave	29/3/13	22/10	95.4		
Blount[48]	10/5 a wave	29/0/9	22/9	96		

M, mean pressure;* not entered; F.O., foramen ovale; A.S.D., atrial septal defect.

† When two pressures are listed, the first is that of the proximal right ventricle, the second that of the distal chamber.

tion of promoting pulmonary flow in some instances. Of the catheterized cases that have been autopsied, the few without defects in the atrial septum had the highest peak pressures in the right atrium.

Closure of the atrial defect was performed in 1 case[38] with symptomatic improvement. This procedure would not be expected to be satisfactory, however, in patients with marked tricuspid regurgitation.

Right ventricular systolic pressure has not been significantly elevated in any case. The abnormal systolic ejection contour is delayed in onset and in reaching a peak.[48] Several authors have reported elevated end-diastolic pressures, which in some instances may represent the transmitted atrial wave.

The pulmonary artery was entered in 27 cases. In none was there a significant gradient across the pulmonary valve.

Ebstein's anomaly may be compatible with considerable longevity, as evidenced by 2 patients who survived to the eighth decade[27, 47] and 4 who were in their sixth and seventh decades.[2, 6, 18, 46] However, of 48 patients who have died, 40 per cent died before the age of 10 years and an additional 30 per cent by the age of 20.

Ten patients died apparently as a direct result of a diagnostic or operative procedure. Four died as a result of cardiac catheterization and 1 following angiocardiography. In 5 published cases operative procedures were undertaken. Presumptive diagnoses in these cases were tetralogy of Fallot and pulmonic stenosis. Shunt procedures in 3,[21, 34] exploratory thoracotomy 1,[23] and induction of anesthesia in 1[32] resulted in death. Because of these experiences such procedures are undertaken with some concern, and a diagnosis made by clinical means becomes of more than academic interest.

Sudden death occurred in 7 patients;[4, 8, 13, 17, 21, 26, 49] cardiac arrhythmias may have been the cause.

Central nervous system complications have been described: cerebral embolism[14] was the supposed cause of death in 1; 2 patients died with brain abscesses,[7, 28] and another with meningitis.[7]

Tuberculosis was a common cause of death in the earlier cases.[1, 3, 8, 9, 12] Two patients died with myocardial infarction,[19, 35] and 2 in congestive failure without other associated cause of death.[11, 43]

Pathology

We have gathered 48 descriptions of postmortem specimens, including our own. The hearts were well over normal weight and pathologic change was generally limited to the right side.

The primary abnormality appeared to lie in the development of the tricuspid valve, the papillary muscles, and the chordae tendineae. The valve leaflets were abnormal in origin and structure, arising in whole or in part from the wall of the ventricle below the valve ring. In structure they varied from small nubbins to large membranous curtains that fused so as to allow communication only through small fenestras. They were occasionally plastered down to the wall of the right ventricle to form an obviously insufficient valve. Cusps in some instances were completely absent. Most commonly the posterior and medial leaflets were grossly deformed but the anterior leaflet was frequently involved as well. In the region of the abnormal cusp, the papillary muscles and chordae were invariably poorly formed, sparse, vestigial, or absent.

The right ventricle was divided into 2 parts by the abnormal valve. The proximal portion was a thin-walled, dilated chamber that had taken on the characteristics of the atrium. The right atrium was hugely dilated and frequently hypertrophied. No specific histologic defect has been noted in the myocardium of the proximal right ventricle. The distal portion was frequently limited to the outflow chamber. Usually its wall was of normal thickness. In 6 instances[23, 29, 43] including 3 of our own, this distal chamber was found to be dilated and the pulmonary valve dilated or thickened; in 3 of these congestive failure was clinically well documented.

A patent foramen ovale was observed in 29 cases, an atrial septal defect in 6. Thus, the mechanism for a right-to-left shunt was present in a large number.

Associated cardiovascular abnormalities have not been commonly reported: a probe-patent ductus arteriosus was found in 1 of our cases and a hypoplastic aorta with fetal coarctation in another.

Differential Diagnosis

The differential diagnosis is of considerable importance, since no established surgical procedure is available in Ebstein's anomaly and exploratory thoracotomy is probably unusually hazardous.

Tetralogy of Fallot may be differentiated by a clinical course in which squatting, syncopal spells, dyspnea, and stunted growth are more prominent. Diastolic murmurs are uncommon; the electrocardiogram shows less block and more evidence of right ventricular hypertrophy; cardiomegaly is uncommon and a coeur en sabot rather than a globular contour is typical.

Tricuspid atresia usually is accompanied by

earlier and more marked symptoms, particularly cyanosis, dyspnea, poor growth, and limited activity. The electrocardiogram also shows large P waves but the considerable right intraventricular block is not usually present; left ventricular dominance or hypertrophy is the rule. The cardiac contour is also quite different in that it has a straight right border or it mimics dextrocardia or coeur en sabot.

Severe pulmonic stenosis with intact ventricular septum, particularly when a right-to-left shunt occurs at the atrial level, represents the most difficult differential diagnosis. The similarity in radiologic appearance has been noted. The typical stenotic, well-transmitted systolic murmur at the pulmonic area accompanied by a thrill, absent diastolic murmur, the observation of presystolic pulsation in neck veins or liver, coupled with definite right ventricular hypertrophy by electrocardiogram usually identifies the malformation. On occasion cardiac catheterization may be the only means of differentiation; to date, elevated right ventricular systolic pressure and a significant gradient across the pulmonary valve have not been described in Ebstein's syndrome.

The auscultatory findings suggest complete transposition of the pulmonary veins. Marked right ventricular hypertrophy by electrocardiogram and engorged pulmonary vascular markings by x-ray differentiate this condition. Blount has pointed out the similarity of auscultatory findings in adult patients to those of rheumatic heart disease.[48]

Summary

Ten cases of Ebstein's anomaly of the tricuspid valve have been presented. The findings in these cases have been correlated with those reported in the literature to emphasize certain clinical features that are of diagnostic value. 1. Symptomatology is usually mild with cyanosis, dyspnea, fatigability, and commonly a history of bouts of palpitation. 2. The physical findings are characterized by normal growth, frequent cyanosis and infrequent clubbing; a quiet cardiac impulse and a systolic thrill between xiphoid and apex; a triple or quadruple rhythm, a second sound diminished at the pulmonary area, and a combination of systolic and diastolic murmurs maximal at the lower left sternal border or apex. 3. Phonocardiographic studies confirm the presence of a triple or quadruple rhythm, show a delayed first sound of normal intensity, demonstrate a systolic murmur of moderate intensity and medium frequency, and a presystolic murmur at the lower left sternal border and apex. Less constant is a mid-diastolic murmur in this area. 4. The characteristic electrocardiogram has tall P waves, frequently prolonged atrioventricular conduction, considerable right bundle-branch block, and right ventricular potentials of low amplitude. 5. By radiologic examination marked cardiomegaly is seen, a contour consistent with right-sided enlargement, a narrow base, diminished pulmonary vascular markings, and poorly delineated pulmonary artery. 6. Angiocardiography reveals a huge right atrial chamber with delayed emptying, poorly opacified pulmonary radicles, and frequent evidence of a right-to-left shunt. 7. Cardiac catheterization demonstrates a large atrium, displacement of the tricuspid valve to the left, moderately elevated right atrial pressure, normal right ventricular systolic pressure and absence of a significant gradient across the pulmonary valve. Peripheral arterial oxygen unsaturation is usual.

The importance of clinical recognition of this entity is stressed in view of the definite hazard involved in undertaking cardiac catheterization and surgical procedures in these patients.

Summario in Interlingua

Es presentate dece casos de anomalia de Ebstein del valvula tricuspide. Le constatationes in iste casos es correlationate con le datos reportate in le litteratura pro signalar emphaticamente certe aspectos clinic que es de valor diagnostic.

1. Le symptomatologia es usualmente leve, con cyanosis, dyspnea, fatigabilitate, e communmente un historia de episodios de palpitation. 2. Le constatationes physic include characteristicamente un normal crescentia, frequentia de cyanosis, e infrequentia de digitos hippocratic; un quiete impulso cardiac e un fremito systolic inter xiphoide e apice; un rhythmo triple o quadruple, un secunde sono

diminuite al area pulmonar, e un combination de murmures systolic e diastolic que es maximal al margine sternal sinistro-inferior o al apice. 3. Studios phonocardiographic confirma le presentia de un triple o quadruple rhythmo. Illos monstrava un retardate prime sono de intensitate normal, un murmure systolic de intensitate moderate e frequentia intermediari, e un murmure presystolic al margine sternal sinistro-inferior e al apice. Un murmure mediodiastolic in iste area es minus constante. 4. Le electrocardiogramma typic es characterisate per alte undas P, frequentemente per prolongate conduction atrioventricular, per considerabile grados de bloco de branca dextere, e per potentiales dextero-ventricular de basse amplitude. 5. Le examine radiologic revela marcate grados de cardiomegalia, un contorno compatible con allargamento al latere dextere, un base de largor reducite, diminuite marcas pulmono-vascular, e un delineation pauco clar del arteria pulmonar. 6. Le examine angiocardiographic revela un enorme camera dextero-atrial con retardo de vacuation, imperfecte opacification del radiculos pulmonar, e frequentemente signos de un derivation dextero-sinistre. 7. Catheterisation cardiac demonstra un grande atrio, displaciamento del valvula tricuspide verso le latere sinistre, elevation moderate del pression dextreo-atrial, normal nivellos del pression systolic dextero-ventricular, e absentia de un gradiente significative trans le valvula pulmonar. Non-saturation oxygenic in le arterias peripheric es le regula.

Le importantia del recognition clinic de iste entitate es sublineate in vista del definite hasardo representate per le execution de catheterisation cardiac o de operationes chirurgic in casos de iste genere.

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Study of the Hemodynamic Effects of the Aorto-Coronary Sinus Graft Operation in Patients with Coronary Artery Disease

By T. W. Moir, M.D., and W. H. Pritchard, M.D.

A group of patients with coronary artery disease have been studied preoperatively and after surgical creation of an arteriovenous fistula between the descending aorta and coronary sinus (Beck II, revascularization operation). Preoperatively, basal studies of cardiac output and blood volume were done with radioisotope technics. Postoperatively, catheterization studies of cardiovascular function were obtained and abnormalities, including heart failure, were found in patients with functionally significant arteriovenous fistulas.

A CLINICAL evaluation of surgical procedures for revascularization of the heart in 63 patients with arteriosclerotic heart disease with angina pectoris has been reported recently by Feil and associates.[1] Two different surgical procedures were utilized after each had been studied extensively in normal dogs.[2, 3] Although the results in 6 patients who had pericardial abrasion, asbestos application to the abraided epicardium, and partial ligation of the coronary sinus were reported, the report emphasized the clinical results in 57 patients who had arterialization of the coronary sinus through a vein graft from the aorta. This paper is concerned primarily with the patients in the latter group who had arterialization of the coronary sinus as described by Beck.[2]

This surgical procedure was performed in 2 stages: (1) a homologous vein graft was first placed between the aorta and the coronary sinus (fig. 1); and (2) after a period of from 2 to 4 weeks, the coronary sinus near its entry into the right atrium was narrowed, allowing a variable arterial flow into the right atrium to remain.

The purposes of the present study were to evaluate certain measures of basal cardiac function in some of these patients with coronary artery disease before surgery and to ascertain the hemodynamic consequences of the surgically created arteriovenous fistula upon the circulation of these subjects.

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Patients and Methods

It was not possible to study a representative sample of patients undergoing the 2-stage operation sequentially at appropriate times before and after operation. Many of the patients studied preoperatively were not restudied after surgery because of nonpatency of the vein graft, operative mortality, or loss from the study for other reasons. Similarly, some of the postoperative patients who had had a successful graft procedure had not been studied preoperatively. Since our primary interest was in the effects of the fistula, patients who survived and achieved a functionally patent graft were studied regardless of whether a preoperative study had been performed.

All patients had coronary artery disease manifested by angina pectoris or previous myocardial infarction, or both. None had preoperative evidence of cardiomegaly or clinical evidence of cardiac failure. All were normotensive.

Patients were studied in the postabsorptive, basal state. Preoperatively, cardiac output was calculated from arterial dilution curves, following injection of iodinated (I^{131}) human serum albumin.[4] Blood volume was determined before and after operation with the same isotope.[4]

Postoperatively cardiac catheterization was performed to study pressure and flow relationships. Pressures were recorded with Sanborn electromanometers, and cardiac output was estimated by the Fick principle. Oxygen consumption was measured by analysis of expired gas while the subject breathed room air. The systemic arteriovenous difference was calculated from the femoral artery oxygen content and the averaged values of the oxygen content of superior and inferior cavae. The pulmonary arteriovenous difference was calculated

FIG. 1. Posterior view of the heart showing vein graft in place between the descending aorta and the coronary sinus. The constricting ligature placed around the coronary sinus (stage II) is not shown.

from the femoral artery oxygen content and the best mixed sample beyond the right atrium, usually the pulmonary artery, but occasionally the right ventricle. Thus, the shunt flow was the difference between calculated pulmonary and systemic flow. Cardiac work was calculated in Kg. M./hr., from the relationship, work = total cardiac output × mean arterial pressure. The kinetic factor, $\frac{mV^2}{g}$, was not used. Total peripheral resistance was calculated by the formula:

$$T.P.R. = \frac{\text{Mean arterial pressure} \times 1332}{\text{Cardiac output (ml. per second)}}.$$

In the postoperative catheterization study 3 groups were designated: 1. *Thrombosed grafts.* These patients had had a vein graft initially placed, but at the second stage operation the communication was found to be thrombosed, or at a later date was completely ligated. In this group no arteriovenous communication was found at the time of the catheterization study. These patients served as controls for the patients with functioning aorto-coronary sinus grafts. 2. *Patent grafts, immediate study.* Catheterization was done from 13 to 28 *days* after placing the graft, and before the second-stage operation. 3. *Patent grafts, remote study.* Catheterization was performed from 11 to 26 *months* after the second stage operation, at which time the coronary sinus had been narrowed at its entrance to the right atrium.

RESULTS

Figure 2 shows the preoperative data for blood volume and cardiac output and demonstrates the wide range of individual determinations. The mean blood volume was 70.3 ± 12.1 ml. per Kg. of body weight. The mean cardiac index was 2.86 ± 0.82 L. per M.² per min. No difference in blood volume or cardiac output was found that could be related to the presence of previous myocardial infarction.

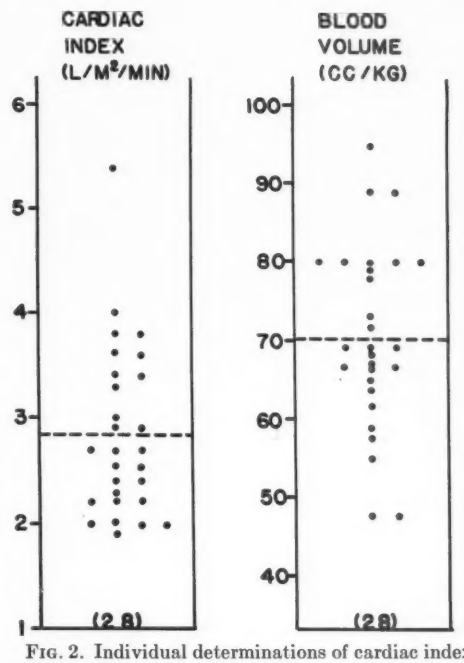

FIG. 2. Individual determinations of cardiac index and blood volume in the preoperative patients. Mean values indicated by dashed line.

Postoperative Studies

Blood Volume. In figure 3 the blood volume-body weight relationship has been plotted and lines of regression have been drawn for the postoperative patients. The blood volume determinations were done at varying times after surgery. Three groups of patients are compared: 17 patients with thrombosed grafts; 13 patients with patent grafts without heart failure; 13 patients with patent grafts with heart failure.

No significant increase in blood volume is discernible in patients with patent grafts when compared with those having thrombosed grafts unless cardiac failure is present. The increase in blood volume in patients with patent grafts

and cardiac failure is significant, p (adjusted means) = <0.01. There was no increase in blood volume in patients with thrombosed grafts when compared to the preoperative study group.

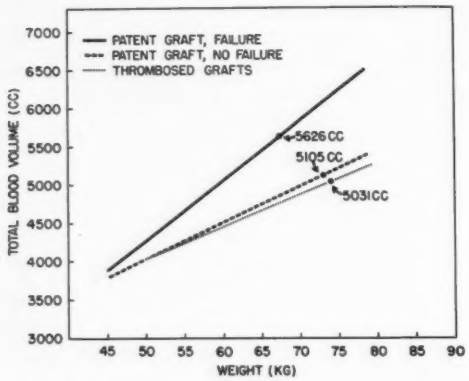

FIG. 3. Lines of regression for individual blood volumes plotted against body weight in the postoperative patients.

Cardiac Output and Shunt Flow. Table 1 shows the individual data and mean values in the postoperative catheterization study. The mean cardiac index in the 6 patients with thrombosed grafts was within normal limits (2.96 L. per M.^{2} per min.) and is comparable to the 2.86 L. per M.^{2} per min. value found preoperatively. In the 6 patients with open grafts catheterized shortly after the first stage of the operation (immediate study group), the cardiac index was slightly elevated, averaging 3.50 L. per M.^{2} per min., and the mean shunt flow was 1.75 L. per min. In the 5 patients with patent grafts of longer duration (remote study group), the cardiac index was markedly elevated, averaging 6.21 L. per M.^{2} per min. with a mean shunt flow of 6.52 L. per min. The effective systemic flow progressively decreased in spite of the augmentation of the total cardiac output in all patients with a functioning shunt and was most pronounced in those patients with grafts of longer duration.

TABLE 1.—*Cardiac Catheterization Data in the Postoperative Patients*

Patient	Mean pressure (mm. Hg)		Cardiac output (L./min.)	Cardiac index (L./M^2 /min.)	Systemic flow (L./ Min.)	Shunt flow (L./ Min.)	Pulse rate	Stroke volume (ml.)	Mean arterial pressure (mm. Hg)	Oxygen consumption (ml./M.^{2}/ min.)	Cardiac work (Kg.M. /hr.)	Systemic A-V difference (vol. %)	Total peripheral resistance (Dynes-cm.-sec.$^{-5}$)	Cardiac failure
	RA	RV												
Thrombosed grafts														
L. G.	4	16	5.26	3.4	5.26	—	60	88	87	180	369	5.0	1325	no
M. M.	4	13	4.85	2.9	4.85	—	104	47	126	137	486	4.8	2070	no
J. D.	3	10	4.65	2.6	4.65	—	60	77	80	116	294	5.0	1375	no
J. S.	8	22	5.95	3.1	5.95	—	98	61	94	132	464	4.2	1250	no
A. J.	2	15	5.50	3.2	5.50	—	75	73	116	122	510	3.8	1680	no
F. M.	7	—	4.70	2.6	4.70	—	98	48	85	145	318	5.4	1440	no
Av.	4.7	15.2	5.15	2.96	5.15	—	82	66	98	139	407	4.7	1523	—
Patent grafts (immediate)														
R. W.	4	—	4.54	2.52	3.95	0.59	75	60	87	136	324	6.0	1530	no
C. N.	12	20	6.90	4.37	4.80	2.10	100	69	74	136	414	4.5	856	yes
J. G.	3	—	4.78	2.78	3.82	0.96	106	45	80	112	310	5.0	1350	yes
C. C.	8	15	6.63	3.50	4.42	2.21	108	61	84	133	444	5.7	1020	no
A. D.	6	15	7.44	3.65	5.78	1.66	105	71	83	140	498	4.9	891	no
J. S.	—	12	8.0	4.2	5.0	3.0	108	74	75	168	518	6.3	565	yes
Av.	6.6	15.5	6.38	3.50	4.62	1.75	100	63	80	137	418	5.4	1035	—
Patent grafts (remote)														
G. P.	4	—	12.7	7.40	4.0	8.7	75	169	94	142	972	6.4	590	no
R. L.	5	10	16.6	8.90	6.8	9.8	70	237	83	135	1110	3.7	400	no
F. L.	15	33	5.56	3.40	3.5	2.0	75	74	100	136	450	6.2	1440	yes
A. J.	5	24	7.70	4.80	3.8	3.9	70	110	98	135	612	6.5	1040	yes
L. O.	14	23	11.2	6.57	3.0	8.2	82	137	84	155	1086	8.9	600	yes
Av.	8.6	22.5	10.7	6.21	4.20	6.52	74	145	92	141	846	6.3	814	—

Three of the 6 patients with patent grafts studied shortly after the first-stage operation were in cardiac failure which developed following surgery. In 2, the cardiac indices were elevated (4.37 and 4.20 L. per M.^{2} per min.). Three of the 5 patients with patent grafts studied in the remote period were also in heart failure at the time of the study. Two of these 3 had increased cardiac indices (4.80 and 6.57 L. per M.^{2} per min.).

Pulse Rate and Stroke Volume. The pulse rate and stroke volume of the patients whose grafts were thrombosed at the time of the study were essentially normal. In those patients with patent grafts of short duration, the stroke volume was not elevated, but there was a consistent increase in pulse rate. The stroke volume became elevated to a mean value of 145 ml. in those patients whose grafts remained functioning from 11 to 26 months; the pulse rate in these subjects was normal.

Intracardiac Pressure. Mean right atrial and right ventricular pressures were normal in the postoperative patients with thrombosed grafts. In the patent graft group, pressures were variably increased and no direct relationship could be found between the volume of shunt flow into the right atrium and right atrial pressure. Rather, atrial pressure was related to mean right ventricular pressure and any increase was due to cardiac failure rather than volume of shunt flow.

Arterial Pressure, Cardiac Work, and Total Peripheral Resistance. Although the mean arterial pressure was, on the average, lower in the patients with patent grafts than in those patients without a shunt, there was no consistent change.

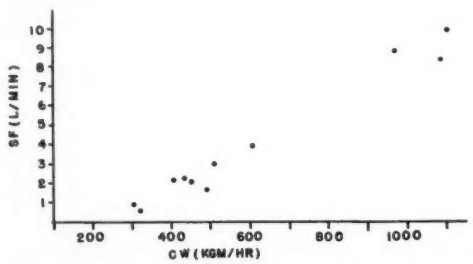

FIG. 4. The relationship between shunt flow and cardiac work in patients with patent grafts.

Cardiac work as shown in figure 4, increased proportionately to the volume of shunt flow in the patients with patent grafts. Peripheral resistance was in the upper ranges of normal in the operated patients with closed grafts, but was slightly lowered in patients with grafts of shorter duration, and decreased in those with shunts present for longer periods of time.

Coronary Sinus Pressure. In 1 patient with a functioning graft, the coronary sinus was catheterized. The coronary sinus pressure was 97/62 (mean 60) mm. Hg; arterial pressure was 140/80 (mean 80) mm. Hg. A blood sample from the coronary sinus was 91 per cent saturated.

DISCUSSION

The study of cardiac output preoperatively demonstrated a mean cardiac index that was in the lower range of normal for the resting state when compared with determinations obtained in normal subjects.[5-8] The results are similar to those of Chapman and Fraser,[9] and indicate that in patients with coronary artery disease, but free of heart failure, the cardiac output at rest is not significantly altered from normal. However, the experience of Smith and associates[6] is at variance with this conclusion.

The mean blood volume of the preoperative patients, expressed in milliliters per kilogram of body weight, was within the limits of normal for the method used.[10, 11] Operation alone caused no significant change in blood volume, since patients with thrombosed grafts had mean blood volume values comparable to the preoperative group.

Of major interest in this study was the opportunity to observe the hemodynamic alterations produced by the aortic-atrial communication in patients with coronary artery disease. Operation per se produced no significant change in the measurements of cardiovascular function, since these values were well within the range of normal in the patients with thrombosed grafts. However, in the patients with patent grafts circulatory abnormalities incident to the arteriovenous fistula became apparent.

It is now generally held that the cardiac output is elevated in the presence of an arterio-

venous fistula. Animal and human studies support this view.[12-15] The present study confirms the fact that this augmentation of cardiac output is due to an increased stroke volume when the shunt flow is of great magnitude. However, in our patients with patent grafts of short duration, and with a relatively low volume of shunt flow, the cardiac output rose only moderately and was due to an increase in pulse rate. As the volume of shunt flow through the patent aorto-coronary sinus fistula increased, cardiac output rose as the result of an increased stroke output (table 1).

Considerable speculation remains concerning the reason for augmentation of stroke volume in arteriovenous fistulas,[16, 17] and particular attention has been directed toward the role of an increased pressure gradient between the right atrium and ventricle.[13, 15, 18, 19] The present study in patients with coronary disease showed no obvious relationship between an increase in cardiac output and mean right atrial pressure; elevations in right atrial pressure were more related to the right ventricular pressure than to the volume of shunt flow and consequent increases in cardiac output. Mean pressure in the atrium, however, may not mirror end-diastolic pressure or volume in the ventricle.[13] In addition, the presence of cardiac failure in some of the patients in the present study vitiates any firm conclusions regarding pressure-volume changes between the right atrium and ventricle relative to increase in stroke volume.

In spite of augmentation of the total cardiac output in these patients, the effective systemic flow was decreased, the degree of which was inversely related to the volume of shunt flow. Similar changes have been described in experimental studies where "body flow" has shown a progressive decrease as the volume of shunt flow has increased.[15]

It is generally believed that the blood volume is elevated in the presence of functionally significant arteriovenous fistulas and it has been suggested that this may be an essential factor in the maintenance of an effective "body flow" in the presence of large fistulas. In experimental animals it has been shown that this rise in blood volume is due to an expanded plasma volume.[20] In human subjects with arteriovenous fistulas, an elevation in blood volume has been

TABLE 2.—*Hemodynamic Data before and after Surgical Obliteration of the Fistula, in a Postoperative Patient in Heart Failure*

	Open	Closed
Cardiac output (L./M.²/min.)	4.8	3.2
Systemic output (L./M.²/min.)	2.2	3.2
Shunt flow (L./min.)	3.9	—
Right atrial pressure (mm. Hg)	7/3 (5)	3/1 (2)
Right ventricular pressure (mm. Hg)	60/5(24)	38/4(15)
Arterial pressure (mm. Hg)	150/70 (99)	156/96(116)
Cardiac work (Kg.M./hr.)	612	510
Total peripheral resistance (dynes-cm.-sec.$^{-5}$)	1040	1680
Blood volume (ml./Kg.)	83	73

variable and inconstant; Warren and associates[21] found only 44 per cent of their patients with any significant blood volume increase, with no good correlation of this change with the magnitude and duration of shunt flow. This elevation of blood volume was observed in the absence of detectable cardiac failure. Epstein, Post, and McDowell[22] have demonstrated decreased renal excretion of sodium in patients with arteriovenous fistulas, and in Hilton's[23] study in dogs, arteriovenous fistulas led to renal vasoconstriction, reduced glomerular filtration rate, and a decrease in sodium, chloride, and water excretion. In these data one finds a suitable setting for fluid retention with subsequent blood volume expansion without cardiac failure. However, in the present study the elevation of blood volume was related to the presence of cardiac failure and lends support to the thesis of Reid and McGuire[14] that elevation of the blood volume in arteriovenous fistulas is due to cardiac failure, at least in patients with pre-existing heart disease.

Since the cardiac work increased proportionally to the volume of shunt flow, the precipitation of cardiac failure in some of these patients is not surprising. However, the incidence of overt heart failure could not be entirely correlated with the volume of shunt flow and it would appear that a major determinant of cardiac decompensation in these patients with coronary disease was the poor "functional reserve" of the myocardium. It is apparent that this surgical procedure, which increases cardiac

work due to the arteriovenous fistula, may precipitate cardiac failure in patients with myocardial disease. Table 2 illustrates studies performed in a patient whose graft remained open and who 18 months after operation developed congestive heart failure. The patient was subsequently reoperated upon, and the fistula was closed; the signs of cardiac failure, together with the hemodynamic abnormalities, regressed.

It is interesting that the volume of shunt flow through the aorto-coronary sinus graft increased with time and resulted in a markedly elevated cardiac output in the patients with grafts of long duration (table 1). If we may assume that the coronary sinus has remained narrowed at its egress into the right atrium, it appears likely that the progressive enlargement of a collateral venous bed in the area of the aorto-coronary sinus graft accounts for the augmentation of shunt flow. Such venous collateral circulation is known to occur in peripheral arteriovenous fistulas in man and has been observed in animals subjected to the present operative procedure.[24]

Summary

A group of patients with coronary artery disease in whom an aorto-coronary sinus graft was surgically created have been studied to determine the functional effects on the cardiovascular system. Preoperatively, mean values for basal cardiac output were within the lower ranges of normal and the average blood volume values were normal.

Postoperatively, no circulatory abnormalities were demonstrated in patients in whom the aorto-coronary sinus graft was thrombosed at the time of study. In those patients with patent grafts, hemodynamic changes of an arteriovenous fistula were demonstrated. Cardiac output and work increased, effective systemic flow decreased, peripheral resistance fell, and blood volume became greater. The increase in cardiac output was related to an increase in pulse rate in cases with small shunt flows and to augmentation of stroke volume when fistulas were of greater magnitude and duration. Elevation of the total blood volume was shown to be related to the presence of cardiac failure and not to the presence of the arteriovenous fistula per se.

Cardiac failure developed in some of the patients with a functioning aorto-coronary sinus graft and could be reversed with subsequent surgical obliteration of the shunt. The development of cardiac failure in these patients with pre-existing heart disease could not be entirely related to the volume or duration of shunt flow, but rather seemed dependent on a lack of "myocardial reserve" to withstand the added load of an arteriovenous fistula.

Increase in volume of shunt flow was related to duration of the functioning aorto-coronary sinus graft and suggested increased venous collateral flow into the right atrium.

Acknowledgment

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Summario in Interlingua

Un gruppo de patientes con morbo de arteria coronari in qui un graffo de sinus aorto-coronari habeva essite create per un operation chirurgic esseva studiate con le objectivo de determinar le resultante effectos in le systema cardiovascular. Ante le operation, le valores medie del basal rendimento cardiac esseva basse-normal, e le valores del volumine medie de sanguine esseva normal.

Post le operation, nulle anormalitates circulatori esseva demonstrate in patientes in qui le graffo aorto-coronari esseva thrombotisate al tempore del studio. In patientes con graffos patente, alterationes hemodynamic de un fistula arterio-venose esseva demonstrate. Le rendimento e le labor cardiac se augmentava, le effective fluxo systemic se reduceva, le resistentia peripheric se reduceva, e le volumine de sanguine se augmentava. Le augmento del rendimento cardiac esseva relationate a un acceleration del pulso in casos con pauc fluxo derivational e a augmentation del volumine per pulso quando le fistulas esseva plus considerabile in magnitude e duration. Esseva monstrate que le augmento del volumine de sanguine total

esseva relationate al presentia de disfallimento cardiac e non al presentia de un fistula arterio-venose per se.

Disfallimento cardiac se disveloppava in certes del patientes con functionante graffos de sinus aorto-coronari e poteva esser revertite per le subsequente obliteration chirurgic del derivation. Le disveloppamento de disfallimento in iste patientes con pre-existente morbo cardiac non esseva completemente relationabile al volumine o al duration del fluxo derivational sed pareva depender plus tosto de un manco de "reservas myocardial" capace a manipular le carga additional de un fistula arterio-venose.

Le augmento del volumine del fluxo derivational esseva relationate al duration del functionante graffo de sinus aorto-coronari e suggereva un augmento del fluxo collateral venose a in le atrio dextere.

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Arteriovenous Fistula of the Splenic Vessels Producing Ascites

By WILLIAM G. CASSEL, JOHN A. SPITTEL, JR., F. HENRY ELLIS, JR., AND ANDRÉ J. BRUWER

Arteriovenous fistula involving the portal vein or its tributaries is a rare condition that in some cases can be treated successfully by surgery if it is recognized. The clinical manifestations and diagnostic criteria are presented.

THE opportunity to cure ascites is a gratifying clinical experience but is seldom encountered. Recently we have observed and successfully treated a patient with ascites and an arteriovenous fistula of the splenic artery and vein.

Arteriovenous fistulas may occur wherever arteries and veins lie in proximity. The usual clinical manifestations, such as thrill, machinery murmur, increased venous pressure with its sequelae in the involved region, and at times cardiac enlargement and failure, are well known. An arteriovenous communication between a systemic artery and the portal vein or one of its tributaries quite logically might produce portal hypertension and its sequelae. Sigwart[1] reviewed the literature prior to 1953 and found 3 cases[2-4] of splenic arteriovenous fistula reported in detail and another[5] mentioned, and he added 1. In 1955 Stener[6] reported a case. Of these, only 1, the patient of Goodhart,[3] had ascites, while 4 patients presented with repeated gastrointestinal bleeding from esophageal varices.[1, 3, 4, 6] Two instances of hepatoportal arteriovenous fistula have been reported[7, 8] and 1 of these patients had ascites.[7]

CASE REPORT

A 34-year-old housewife came to the Mayo Clinic on October 29, 1956 because of swelling of the abdomen of 4 to 5 weeks' duration. Three months prior to admission her third pregnancy was terminated normally. The pregnancy was complicated by hypertension and by edema of the ankles during the eighth and ninth months. For 2 months post partum she felt well. Four to 5 weeks prior to admission she noted rapid increase in the size of her abdomen unaccompanied by dyspnea, peripheral edema, fever, or pain. Two to 3 weeks prior to admission anorexia nausea, and vomiting developed and she noted a full sensation in her abdomen. X-ray studies revealed the presence of calcified cyst-like structures in the left upper quadrant of the abdomen. Laparotomy was performed on October 26, 1956, with a preoperative diagnosis of pancreatic cyst. After 4,500 ml. of straw-colored ascitic fluid were removed, the left kidney was seen to be depressed by a cystic mass that was said to involve the left kidney and to be fixed to the spleen. Aspiration of the mass disclosed blood. Further exploration was not performed and the abdomen was closed. Three days postoperatively the patient was referred to the Mayo Clinic for further diagnosis and treatment.

The history revealed that 11 years prior to admission the patient had sustained a bullet wound of the left lower part of the thorax. The bullet entered anteriorly at the sixth intercostal space in the midclavicular line, and came out at the costal margin in the left posterior axillary line. The patient was hospitalized and treated conservatively, and recovered in 2 weeks.

Physical examination revealed a slender, chronically ill young woman whose weight was 135 pounds. Entrance and exit scars of the old bullet wound were present on the left lower part of the thorax. There was a recent left abdominal incision. The abdomen was distended, with evidence of free fluid. The edge of the liver, felt 1 to 2 fingerbreadths below the right costal margin, was smooth and nontender. The tip of the spleen was palpable. A continuous multiple-pitched murmur was audible over the left posterolateral part of the thorax about 2 cm. lateral to the bullet scar. The results of physical examination were otherwise negative. There was no peripheral edema, distention of the veins of the neck, or spider angiomas.

Laboratory studies revealed the following: moderate albuminuria with microhematuria; hemoglobin, 12 Gm. per 100 ml. of blood; leukocyte count, 12,100 per mm.^{3}; erythrocyte sedimentation rate, 65 mm. in the first hour (Westergren); flocculation reaction for syphilis, negative; fasting blood sugar, 128 mg. per 100 ml.; blood urea, 38 mg. per 100 ml.; serum bilirubin, negative reaction direct, and 0.9 mg. per 100 ml. indirect; sulfobromophthalein (Bromsulphalein) retention after 1 hour, grade 3 (34 per cent); thymol turbidity, 0 unit; cephalin-cholesterol flocculation, negative; alkaline phospha-

From the Mayo Clinic and the Mayo Foundation, Rochester, Minn. The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

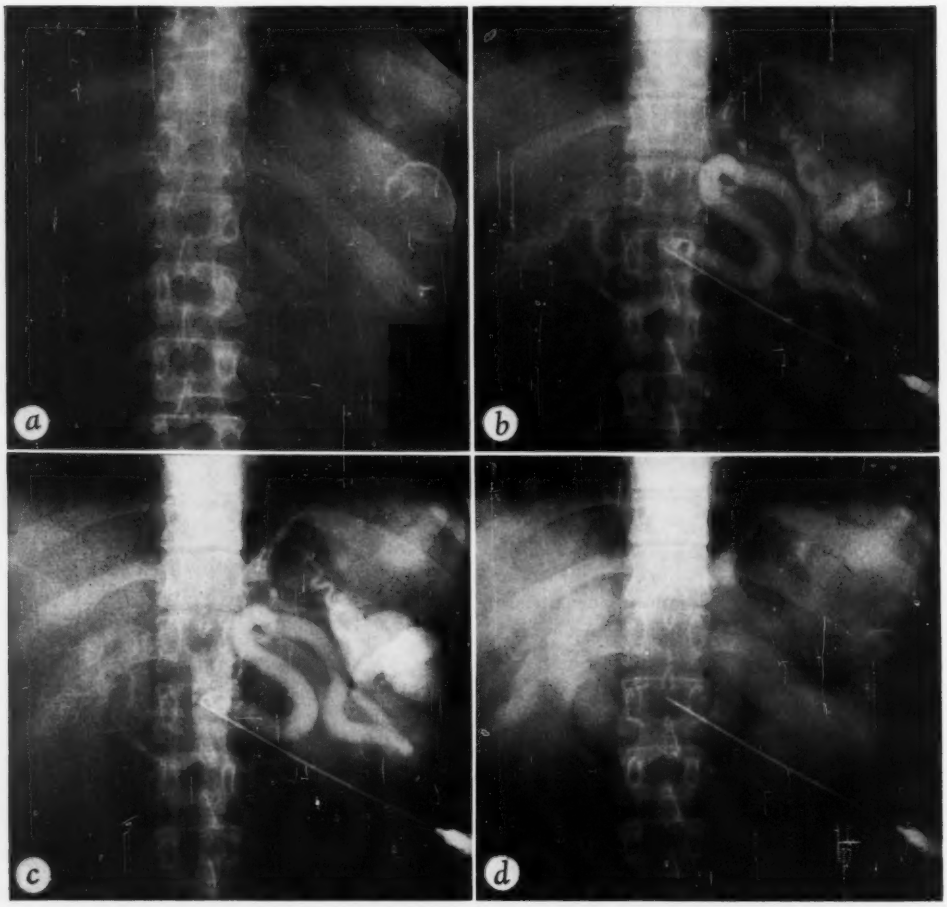

FIG. 1. *a*. Roentgenogram of the abdomen showing crescentic areas of calcification in the left upper quadrant. *b*. Aortogram showing enlarged tortuous splenic artery and opacification within the calcified areas. *c*. Aortogram following second injection of dye. There is opacification of the venous aneurysm adjacent and medial to the calcium-containing aneurysms. *d*. Roentgenogram taken 10 seconds after the one represented in *c*, showing enlarged splenic and portal veins.

tase, 58 King and Armstrong units per 100 ml. of serum; serum proteins, 7 Gm. per 100 ml., with 5 Gm. of albumin and 2 Gm. of globulin.

Roentgenographic examination did not disclose any abnormality of the thorax, but did show linear calcification in the shape of an incomplete oval, measuring 4 by 3 cm., in the left upper quadrant of the abdomen.

Excretory urography showed 2 egg-shaped areas of calcification 4 cm. in diameter in the left suprarenal area (fig. 1*a*). These were thought to be extrarenal, and the upper pole of the left kidney appeared to be compressed as if by a suprarenal mass. Left retrograde pyelographic examination gave no additional information.

Abdominal paracentesis yielded 3,000 ml. of serosanguineous fluid. Culture of the ascitic fluid for bacteria and examination of it for malignant cells gave negative results.

The ascites, the classic murmur of an arteriovenous fistula over the left lower part of the thorax, the calcifications in the left upper quadrant of the abdomen as revealed roentgenographically, and the history of a bullet wound of the left lower part of the thorax 11 years previously suggested a splenic arteriovenous fistula.

Aortography was performed to confirm the clinical impression. Because of the possible danger of passing a needle into an aneurysm, it was decided that aortography performed via a catheter in the

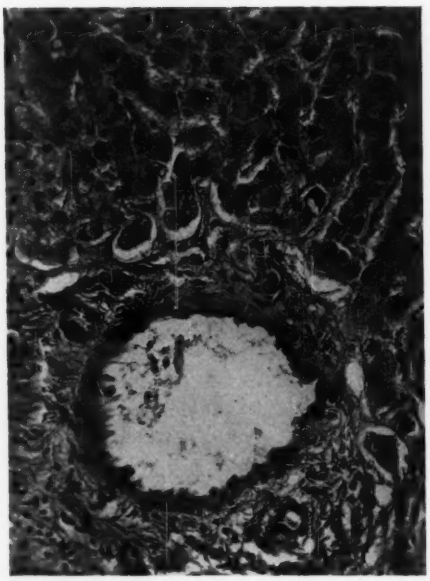

FIG. 2. Biopsy specimen from the liver. The parenchyma is normal (hematoxylin and eosin; × 200).

aorta would be safer than translumbar aortography. However, an attempt to pass a catheter down the descending thoracic aorta via the left brachial artery was unsuccessful. Routine translumbar aortography was therefore performed, the needle being passed into the aorta at the level of the first lumbar vertebra. When the tip of the needle was about half way between the skin and the aorta, blood was aspirated from a low pressure site; it seemed probable that the venous sac of the arteriovenous aneurysm was traversed.

After the needle had been placed in the aorta, two injections of 70 per cent acetrizoate (Urokon) sodium were made. After the first injection, consisting of about 10 ml., the roentgenogram (fig. 1*b*) revealed an enlarged, tortuous splenic artery and dense opacification within the calcified areas in the left upper quadrant. At the end of the second injection, consisting of about 35 ml. of opaque material, the roentgenogram showed that a large uncalcified aneurysm had become opacified adjacent and medial to the calcium-containing aneurysms (fig. 1*c*). Another roentgenogram (fig. 1*d*) taken about 10 seconds after the end of the second injection demonstrated that the opaque material that had pooled in the uncalcified area emptied into the splenic vein, and that the splenic and portal veins were considerably enlarged. It was evident from these studies that

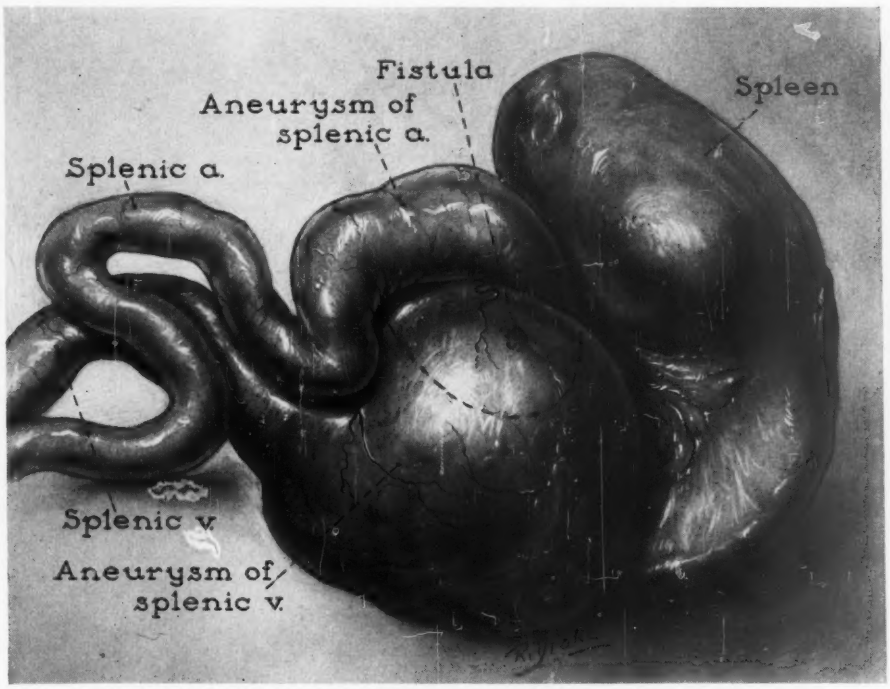

FIG. 3. Drawing of gross specimen.

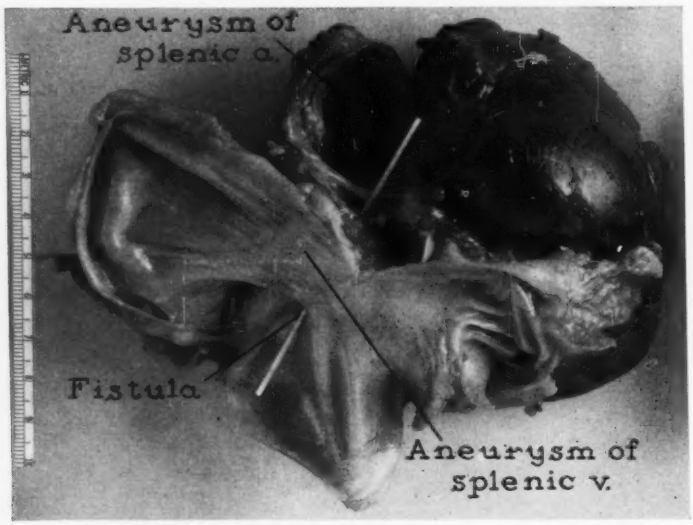

FIG. 4. Opened surgical specimen with probe in arteriovenous fistula.

the calcified shadows in the left upper quadrant were related to the arterial aneurysm and that the even larger venous aneurysm contained no calcium.

All other branches of the abdominal aorta were of normal caliber.

Operation was undertaken on the ninth day after admission. A left thoraco-abdominal incision was made, the old scar being excised and the incision being continued laterally over the costal arch and into the thorax through the seventh intercostal space. The diaphragm was opened partially in the line of the incision.

The liver was tremendously enlarged and the left lobe extended laterally well under the left leaf of the diaphragm. The liver was smooth in contour. Biopsy showed normal hepatic parenchyma (fig. 2). The gastrohepatic omentum was opened and an enlarged, tortuous splenic artery was visualized; this was doubly ligated near its origin. Immediately the continuous murmur audible to the anesthesiologist over the left posterior part of the thorax disappeared. The veins in the mesentery of the small intestine were not dilated. The remainder of the abdomen at exploration appeared normal except for the region of the spleen.

In the hilar region of the spleen a lobulated aneurysm of the splenic artery was visualized, and associated with it was a much larger aneurysm of the splenic vein; the latter aneurysm lay anteriorly and somewhat inferiorly (fig. 3). The spleen was densely adherent to the diaphragm and was dissected away with some difficulty. It was eventually retracted upward and medially, whereupon the aneurysms of the splenic vein and artery were thoroughly exposed. As the dissection continued, a portion of the splenic vein was reached that, although enlarged, was small enough to permit ligation and division. The splenic artery was likewise ligated and divided. It was necessary to remove a portion of the tail of the pancreas as well.

The excised specimen therefore consisted of the spleen, the aneurysms of the splenic artery and the splenic vein, and a portion of the tail of the pancreas. When the specimen was opened, a communication 4 mm. in diameter was found between a bilocular aneurysm of the splenic artery and an aneurysm of the splenic vein (fig. 4). Each locule of the arterial aneurysm measured 4 cm. in diameter, and the venous aneurysm measured 8 by 5 by 5 cm.

The cut end of the pancreas was oversewn, the diaphragm was closed, the costal arch was reapproximated, and the thorax and abdomen were closed.

The patient's postoperative course was uneventful. The mild diabetes, as evidenced by the increased concentration of blood sugar, was managed without incident by a diabetic diet. The platelet count rose from 240,000 per mm.^{3} on November 10 to 572,000 on November 13 and to 653,000 on November 16. A routine urinalysis on November 9 gave negative results. The serum bilirubin reaction remained normal postoperatively, and the concentration of alkaline phosphatase decreased to 38.7 King and Armstrong units per 100 ml. of serum by the tenth postoperative day. Sulfobromophthalein retention at the end of 1 hour on the ninth postoperative day was grade 1 (6 per cent). Three months postoperatively the patient said that she was well and had noted no further ascites.

DISCUSSION

The mechanism of formation of ascites is not fully understood. Volwiler, Grindlay, and Bollman[9] observed in dogs with normal plasma

TABLE 1.—*Features of Reported Cases of Splenic Arteriovenous Fistula*

Author	Age and sex	Gastrointestinal bleeding	Ascites	Bruit	Site of fistula	Miscellaneous
Weigert[2] (1886)	49 F	Not stated	Not stated	Not stated	Hilus of spleen	Cause of death not given. Multiple arteriovenous communications at necropsy.
Goodhart[3] (1889)	49 F	Repeated hematemesis and melena, 5 mo.	Present	Present	2 in. from hilus of spleen	Died from hematemesis. Single arteriovenous communication at necropsy.
Blakemore[4] (1948)	23 F	Repeated hematemesis, 20 yr.	Not stated	Not stated	Not reported adequately	Died postoperatively. Multiple arteriovenous communications. Portal pressure 350 mm. of water.
Sigwart[1] (1953)	25 F	Repeated hematemesis, 9 yr.	Absent	Not stated	In spleen	No gastrointestinal bleeding after removal of arteriovenous fistula and spleen. Portal pressure at operation 430 mm. of water. Single communication.
Stener[6] (1955)	38 F	Repeated hematemesis and melena, 20 yr.	Absent*	Present	Hilus of spleen	No gastrointestinal bleeding after removal of arteriovenous communication and spleen. Multiple arteriovenous communications.
Authors' case	34 F	None	Present	Present	Splenic hilar area, 2 cm. from spleen	Ascites disappeared after removal of arteriovenous communication and spleen. Single arteriovenous communication.

* Ascites occurred postoperatively but was temporary.

protein that there had to be some element of hepatic congestion to produce marked, spontaneous, progressive ascites; such congestion was produced by constriction of the thoracic inferior vena cava. In another group of dogs constriction of the inferior vena cava and portal vein produced slight to moderate ascites when the dogs were made hypoproteinemic by plasmapheresis. Baggenstoss and Wollaeger[10] found ascites in 5 of 15 necropsy cases in which portal hypertension was due to occlusion of the extrahepatic portion of the portal vein and in which there was no complicating disease that might in itself have been a cause of ascites. They concluded that portal hypertension per se was an important factor in the development of ascites in these cases. They found evidence that ascites was more likely to occur when the hepatopetal collateral circulation was inadequately developed.

Schilling and McKee[11] produced hepatoportal arteriovenous fistulas in dogs and found that ascites developed in only 1 of them, this occurring 30 months postoperatively; this animal had evidence of disturbed hepatic function, and microscopic examination of its liver revealed marked scarring and fatty infiltration in many places. Servello and Rossi[12] did not observe ascites in dogs in which they produced splenic arteriovenous fistulas; this fact may be related to the brief period of observation (45 days). They did, however, note hepatic congestion and microscopic evidence of dilatation of the hepatic vascular bed.

Besides our patient, only 1 other patient with arteriovenous communication of the splenic vessels has been reported as having ascites (table 1). Bleeding from esophageal varices, often repeated over many years, was a more common clinical manifestation. Blakemore[4] and Sigwart[1] found an increase of portal pressure in their patients. The typical bruit of an arterio-

venous fistula has been noted in only 3 cases, including the present case.

The cause of the arteriovenous fistulas in the previously reported cases reviewed in table 1 is obscure. Pre-existing trauma is not mentioned in any of them. Three patients had multiple arteriovenous communications and 3, including ours, had a single communication. The existence of multiple communications suggests a congenital origin. In Sigwart's[1] case the communication was single but within the spleen and, in his opinion, was probably congenital. In the 2 cases with multiple communications and in which the history was reported, and in Sigwart's case, evidence of portal hypertension (gastrointestinal hemorrhage) appeared in childhood or early adult life; this suggests a congenital anomaly. Goodhart's[3] patient, the only one other than ours who had ascites, was 49 years old and had hematemesis and melena for only 5 months prior to death; the single arteriovenous communication was likely acquired and possibly the result of rupture of an aneurysm of the splenic artery into the adjacent vein.

The close relationship of the development of ascites to parturition observed in our case suggests the possibility that an aneurysm of the splenic artery ruptured into the splenic vein as a result of changes in intra-abdominal pressure incident to parturition. Owens and Coffey[13] have shown a relationship between pregnancy and rupture of a pre-existing aneurysm of the splenic artery. It is equally possible that the splenic arteriovenous fistula developed in our case at the time the bullet wound was inflicted 11 years prior to the onset of ascites.

Ascites in arteriovenous fistula involving the portal system could be produced by either or both of 2 factors—portal hypertension and hepatic congestion. As previously mentioned, portal hypertension was shown to exist in such cases by Blakemore[4] and Sigwart[1] at the time of operation. According to Baggenstoss and Wollaeger,[10] portal hypertension in itself can cause ascites. In addition, transmission of arterial pressure to the portal system may cause hepatic congestion and ascites in a manner analogous to that in the experiments of Volwiler and co-workers[9] in which occlusion of the thoracic inferior vena cava caused hepatic congestion and massive ascites. Significantly, those patients whose fistulas were presumably congenital did not have ascites. It is possible that in patients with multiple arteriovenous fistulas involving the portal system there is sufficient hepatofugal circulation during the developmental stage to prevent ascites.

Strickler[7] and Madding,[8] with their co-workers, have each recently reported a case of single communication between the hepatic artery and the portal vein, which would provide an analogous alteration in the hemodynamics of the portal vein, namely transmission of arterial pressure to the portal vein. The patient of Strickler and co-workers had ascites and hematemesis. The arteriovenous fistula was thought to have been acquired as a result of rupture of a congenital aneurysm into the portal vein, as may have occurred in Goodhart's case. The patient of Madding and co-workers[8] had gastrointestinal bleeding without ascites. These authors expressed the belief that the arteriovenous fistula was of congenital origin.

In 3 of the reported cases[1, 4, 6] (table 1) and in our case surgical approaches were made. The fistula was successfully removed in 3. In the 2 reported cases of hepatoportal arteriovenous fistula operation was unsuccessful.

When calcium is present in an aneurysm of the splenic artery the diagnosis can be made with considerable confidence by routine roentgenologic methods. In 1932 Lindboe[14] made this diagnosis roentgenologically, and since then the roentgenologic features of such aneurysms have been described repeatedly. There is no reason to believe that the arterial component of a splenic arteriovenous aneurysm, once calcified, should have a different appearance.

Calcium deposition in an aneurysm of the splenic artery usually is manifested as a linear opacity in the shape of a complete or incomplete oval representing shadows caused by the tangential trajectory of the beam. These crescentic densities enclose mottled, ill-defined, calcific densities, representing the regions where the roentgen rays have passed through the aneurysm en face.

Culver and Pirson[15] have indicated that it may take 10 to 20 years for calcification to develop in the walls of an aneurysm of the splenic artery. Particularly in cases prior to calcification, abdominal aortography should be performed on the basis of clinical suspicion.

Furthermore, aortography should always be performed when the question of an intra-abdominal arteriovenous fistula arises, because by this means only can the extent of the uncalcified portion of the lesion be demonstrated preoperatively. In our case the venous (uncalcified) aneurysm was larger than the arterial (calcified) component.

Summary and Conclusions

Arteriovenous fistula involving the portal vein or its tributaries is a rare condition and may be accompanied by ascites. In this paper the reports of 5 cases are reviewed and a new case is reported; in addition, reports of 2 cases of hepatoportal fistula are reviewed.

Ascites, which was reported in 2 of the 6 cases of splenic arteriovenous fistula, may be explained on the basis of portal hypertension or hepatic congestion or a combination of both these factors. It occurred only in patients with a single arteriovenous fistula of the splenic vessels.

In patients with ascites or signs of portal hypertension, arteriovenous fistula involving the portal system should be suspected, particularly if a machinery murmur can be heard or if there is x-ray evidence of calcification in the region of the portal vein or its tributaries. The diagnosis can be established by aortography. Surgical cure is possible in some cases.

Summario in Interlingua

Fistula arteriovenose afficiente le vena portal o su tributarios es un condition rar e pote esser accompaniate de ascites. Le presente articulo passa in revista le reportos de 5 casos e reporta un caso additional. In plus, reportos de 2 casos de fistula hepatoportal es passate in revista.

Ascites, que esseva reportate in 2 del 6 casos de splenic fistula arteriovenose, pote esser explicate super le base de hypertension portal o de congestion hepatic o de un combination de iste factores. Illo occurreva solmente in patientes con un unic fistula arteriovenose del vasos splenic.

In patientes con ascites o signos de hypertension portal, fistula arteriovenose afficiente le systema portal debe esser suspicite, specialmente si un murmure de locomotiva es audibile o si il ha evidentia roentgenologic de calcification in le region del vena portal o su tributarios. Le diagnose pote esser establite per aortographia. Curation chirurgic es possibile in certe casos.

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Mast Cells in the Circulatory System of Man

By O. J. Pollak, M.D., Ph.D.

This report is based upon a study of multiple segments of the cardiovascular system of 200 deceased persons and selected surgical specimens. Mast cells are present in the adventitia of all blood vessels. Only the largest vessels have mast cells in the intima and subintima as well. In this location the number of mast cells is highest in grossly normal but microscopically edematous areas. Mast cells are rarely present in early and are never present in advanced atheromatous lesions. The theory is advanced that mast cells are attracted by plasma insudate to release heparin for degradation of lipoproteins. Thus, mast cells might play a role in atherogenesis.

MUCH has been written about mast cells,[1, 2] but our knowledge is still fragmentary and controversial. References to the presence of mast cells in blood vessels of animals are available[3-11] but there is none regarding their occurrence in vessels of man. A single paper deals with mast cells in the human heart.[12] Lack of information about mast cells in human blood vessels prompted this study.

Materials and Methods

Two hundred patients were studied: 100 white and 30 Negro male subjects, and 42 white and 28 Negro female subjects. The youngest were an infant born dead in the seventh month of fetal life and a pair of full-term twins who lived but 4 hours. The oldest person was 90 years of age. Distribution of subjects over the 9 decades of life was 32, 10, 22, 20, 18, 32, 32, 28, and 6, respectively. The average age was 44 years.

The length of hospitalization prior to death varied widely. Some persons were dead on arrival, some had died a violent death, and others succumbed to various acute or chronic diseases. Causes of death corresponded to general mortality statistics.

Patients' charts and necropsy protocols were studied. All details were recorded for correlation with mast cell studies. Attention was paid to such details as body build and weight, mode and hour of death, interval between last meal and death, alcohol consumption and medication, and time between death and necropsy.

Transverse strips about 2.5 to 3 cm. long and about 0.4 cm. wide were cut from the ascending, thoracic and abdominal aorta. Grossly normal tissue was studied in all cases. Where alterations were visible, strips also were obtained from lesions of varied character. Similar strips were obtained from the main pulmonary artery, the inferior, and superior vena cava.

In each case, rings instead of strips were cut from the right pulmonary artery, left common carotid artery, right renal artery, left common iliac artery, and the portal vein. Normal and altered vessels were collected. Rings, instead of strips, were also cut from the aortas of children.

Selected surgical specimens were studied: 6 varicose veins, 4 femoral and tibial arteries, and once, vessels from a patient with Buerger's disease.

Sections were taken from the heart muscle and coronary arteries of all subjects. Normal and altered heart muscle was sampled.

Tissues were placed into a 4 per cent watery solution of basic lead acetate for 48 hours.[13] They were rinsed twice in 10 per cent formalin solution and then placed for 48 hours in formalin. After fixation, tissues were processed in the usual manner. Paraffin sections, 6 μ thick, were stained with hematoxylin and eosin, with Pollak's trichrome stain,[14] with the Giemsa stain, and in a 1 per cent solution of toluidine blue in methanol. The last 2 methods were found equally satisfactory for demonstration of cells with basophilic granules spoken of as mast cells.

Sections were scanned under the high-power lens of the microscope. Mast cells were localized and their appearance was noted. Mast cells were enumerated in the aortic intima (the endothelium) and subintima (subendothelial layer). No attempt was made to count mast cells in the aortic adventitia. No counts were made in any of the other blood vessels. In each aortic strip, at least 100 fields were scanned to obtain the number of intimal-subintimal mast cells per 100 high-power fields. Cells were counted by moving the slide so that the endothelium was close to the edge of the visual field.

Observations

Aorta. Cells with basophilic granules were found in the intima, the subintima, and the adventitia. But for a single slide in which 2 mast cells were seen in a widened space between myofibrils close to the adventitia, the muscularis was always void of mast cells. Adventitial

From the Kent General Hospital, Dover, Del.

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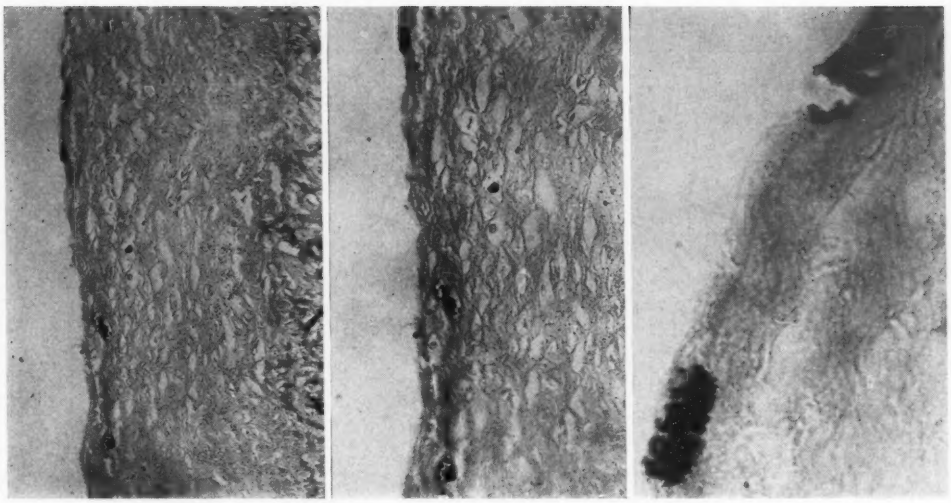

FIG. 1. A visual field of the inner coat of an ascending aorta. Left, × 200; middle, × 420; right, × 1100, Giemsa stain. Note the location of mast cells in the edematous intima-subintima, the round shape of one of the subintimal mast cells and the oval shape of the other mast cells, the lesser density of granules in subintimal mast cells compared to intimal mast cells, and the vacuolization of one intimal mast cell.

mast cells were in close proximity to vasa vasorum and were found in all slides, regardless of findings in the inner wall of the aorta.

Most of the mast cells were in the endothelium proper and in the upper layers of the subintima. Except for the basophilic granules they resembled endothelial cells. Fewer mast cells were present in the lower half of the subintima. In this location they were more round and their granules were less dense, as compared to cells located closer to the vascular lumen. The size of granules and their staining ability were the same in all mast cells, but some had a single large vacuole.

Grossly Normal Aorta. The number of intimal-subintimal mast cells varied from person to person, from one aortic sector to the other, and from one visual field to the next. In slides from 36 subjects, 14 of whom were less than 20 years old, no mast cells were found. (Possibly, these results, as other findings, might undergo revision if one were to scan serial sections.) Differences for the 3 aortic sectors studied being disregarded, from 1 to 10 mast cells were counted in 100 fields in 84 persons, 11 to 20 cells in 56 persons, and between 21 and 90 cells in 24 persons. All subjects with more than 11 mast cells per 100 fields were over 20 years old.

More mast cells were seen in the ascending aorta than in other sectors. Sometimes the thoracic and abdominal aorta had about equal mast cell counts. Usually the count was lowest in the abdominal aorta. Typical examples of the number of mast cells per 100 fields of ascending, thoracic, and abdominal aorta were 33, 24, 13; 53, 25, 10; 99, 40, 18; 146, 54, 32; and 90, 37, 40. Thus, a different average could be arrived at for each sector in every subject, with the highest one for the ascending aorta (fig. 1).

Commonly fields with mast cells alternated with fields without mast cells. The highest total number of fields with mast cells was 50 out of 100. The highest number of consecutive fields with mast cells was 15. Maximum count of mast cells per single high-power field was 8.

The highest concentration of mast cells was seen in areas that, though grossly normal, appeared edematous on microscopic study. This was reflected in mast cell counts per field, per aortic sector, and per subject. In some instances fine basophilic granules were scattered

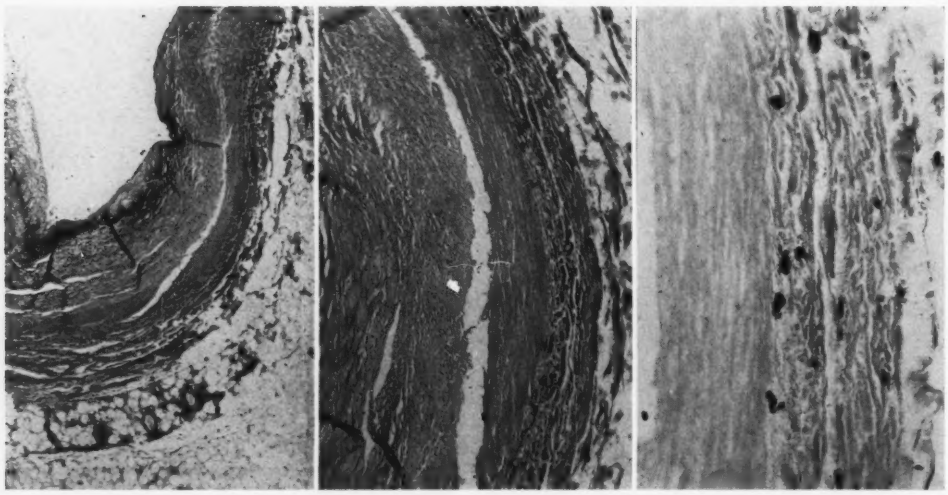

FIG. 2. Coronary artery. Left, × 45; middle, × 125; right, × 250, Giemsa stain. The accumulation of mast cells is close to the outer muscularis.

through edematous, metachromatic subintimal ground substance.

Grossly Abnormal Aorta. As a rule atheromatous plaques were without mast cells. This held true for all organized plaques, whether fibrosed or calcified, without or with parietal thrombi. In most instances early plaques were also without mast cells. A few were found at the edges of an intimal "cushion" in some slides. Lipophages seemed to replace mast cells of the intima-subintima. Between plaques the number of mast cells was the same as in strips obtained from grossly normal areas of the particular aortic sector. Adventitial mast cells were present regardless of intimal alterations.

Intimal-subintimal mast cells from a syphilitic aneurysm of the ascending aorta numbered 33 per 100 high-power fields. In 4 patients with ruptured aneurysm of the descending aorta, mast cell counts were 3, 12, 22, and 40, respectively. Sections from the thoracic aorta perforated by a shot had only 5 mast cells in the inner aortic wall. There were 16 mast cells per 100 fields in sections from the thoracic aorta with a transverse tear sustained in an automobile accident. The number of adventitial mast cells was about the same in damaged parts and unharmed parts of the aorta in all patients.

Other Arteries. In the main pulmonary artery the number of intimal-subintimal mast cells was about the same as in the thoracic aorta of each subject. None of the arteries of smaller caliber had mast cells in the inner coat. In the adventitia of all these arteries mast cells were abundant. Findings were the same in grossly normal and abnormal sectors, with the exception of *coronary arteries*, where adventitial cells were more numerous around atheromatous vessels than around normal ones. The outer muscularis of altered coronary arteries was usually besieged by mast cells (fig. 2).

Femoral and tibial arteries, intact, with atheromatosis, free, or thrombosed were surrounded by mast cells. Arteries and veins from a patient with advanced obliterating thromboangiitis had no mast cells in the inner coat but quite a few in the adventitia.

Veins. The inferior and superior venae cavae had mast cells in the inner layers but saphenous veins had none. All veins had many adventitial mast cells. In the large veins mast cells were located mainly in the deeper layers of the subintima and numbered at least as many as in the ascending aorta from the same person. Often there were almost twice as many mast cells in the large veins as in the aorta. Mast cells were more plentiful in the inferior vein than in the superior vein. The portal vein was

always surrounded by mast cells but none was found in the intima.

Heart. In normal portions of the heart mast cells were seen in the interstitial tissue and the epicardium, often in proximity to small blood vessels. In recently infarcted areas (18 patients) the number of mast cells was the same as in adjacent normal areas. Organized infarctions were without mast cells (16 patients) save for isolated cells at the periphery of scar tissue. In the heart of a patient who died of rupture of a recently infarcted left ventricle, mast cells were as numerous in the lacerated as in intact tissue. Average mast cell counts in the aortas of patients without, with recent, or with old myocardial infarction were about equal.

Discussion

It is debatable which of the following should be considered the normal for aortic intima-subintima: absence of mast cells, presence of a few mast cells, or presence of numerous mast cells. In small animals (frog, rat, guinea pig, rabbit) mast cells were found in the adventitia only, while these cells were seen in the aortic intima of large animals (cow, calf, horse, dog, pig). We observed that children had no, or but few, aortic intimal mast cells; also that only large blood vessels had mast cells in the inner coat. A physiologic relationship between intimal mast cells and the caliber of blood vessels seems likely.

The origin of tissue mast cells is a matter of dispute. Identity of tissue mast cells with circulating basophils is suggested by location of mast cells in and around blood vessels. Origin of tissue mast cells from connective tissue cells has been widely accepted. The suggestion of epithelial origin of mast cells[15] might deserve more attention. The position of mast cells between intimal endothelium cells and their structural resemblance to these cells is intriguing.

Correlation of counts of aortic mast cells with clinical and necropsy data was unsuccessful. Attention is focused on the observation that high mast cell counts were obtained from fields with edematous tissues. Focal intimal-subintimal edema is often seen in grossly intact blood vessels of persons who died in shock.[16] In our series, all subjects in whom mast cell counts were high had experienced shock, but not all persons who had been in shock had high aortic mast cell counts. Some persons may have died too quickly, before an increase of mast cells could take place. Other persons recovered from shock; mast cells could have appeared and disappeared, degranulated, or disintegrated. Such speculation finds support in the observation of extracellular basophilic matter in edematous ground substance.

Multiple reports concern a reduction of basophils during stress[1] and in experimental shock.[17] Disintegration of tissue mast cells following stress,[1] adrenocorticotropic hormone injection,[18] cortisone medication,[19-22] or adrenalectomy[2] was observed. Cortisone effect was, however, denied by some authors,[2, 23, 24] A link between mast cells and shock has been established, but the nature of the relationship is not clear.

Shedding of granules of tissue mast cells in response to a variety of stresses has been reported[25] and various functions have been ascribed to these cells. Apparently mast cells have multiple functions: uptake, transport, and release of macromolecular matter, such as histamine,[26] heparin-histamine,[27] or hyaluronic acid.[28] Parallel increase in these substances and in mast cell counts need not be interpreted as evidence that mast cells are the source of these substances.

Highest counts of aortic mast cells were obtained in patients whose blood plasma was milky at autopsy. A man weighing close to 300 lb. who died in shock following an accident had 150 mast cells per 100 high-power fields in the intima-subintima of the ascending aorta. Possibly mast cells are attracted by lipoproteins carried into the vessel wall by blood plasma insudate. This thought finds support in the results of experiments. Intraperitoneal injection of fat to rats caused an increase in mast cells and severe degranulation.[29] Upon intracorneal injection of serum lipoprotein fractions to dogs mast cells appeared in edematous tissues where normally none was found.[30] Heparin carried and released by tissue mast cells might serve to break down lipoproteins into soluble protein and insoluble lipids. The presence of mast cells in edematous tissues and their absence in

atheromatous plaques possibly implicate these cells as participants in atherogenesis.

Summary

Mast cells were studied in grossly normal and grossly altered segments of the heart, aorta, pulmonary artery, the venae cavae, and multiple smaller blood vessels of 200 deceased persons. Vessels were also studied in 11 surgical specimens. They were counted in the inner layer of the ascending, thoracic, and abdominal aorta. The number was expressed per 100 high-power fields in each sector. Observations on the absence, presence, and quantitative differences of intimal-subintimal mast cells in various parts of the cardiovascular system are reported. Interpretation is attempted of the observation of the presence of mast cells in the inner coat of large vessels, their absence from small vessels, and their frequency in edematous areas of the intima-subintima and absence or rarity in atheromatous lesions.

A theory concerning the quantitative increase and function of mast cells is advanced.

Summario in Interlingua

Mastzellen esseva studiate in macroscopicamente normal e macroscopicamente alterate segmentos del corde, del aorta, del arteria pulmonar, del venas cave, e de varie vasos minor de 200 personas decedite. Esseva etiam studiate le vasos de 11 specimens chirurgic. Le mastzellen esseva contate in le strato interior del aorta ascendente, descendente, e abdominal. Lor numeros esseva exprimite in tantos pro 100 campos a alte potentia in omne sector. Es reportate observationes in re le absentia, presentia, e le differentias intimal-subintimal de mastzellen in varie partes del systema cardiovascular. Es tentate un interpretation del observation del presentia de mastzellen in le tunica intime del grande vasos, de lor absentia in vasos minor, e de lor frequentia in areas edematose intima-subintimal e absentia o raritate in lesiones atheromatose.

Es formulate un theoria in re le augmento quantitative e le function de mastzellen.

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A thing is important if any one think it important. The process of history consists in certain folks becoming possessed of the mania that certain special things are important infinitely, whilst other folks cannot agree in the belief. The Shah of Persia refused to be taken to the Derby Day, saying, "It is already known to me that one horse can run faster than another." He made the question "which horse?" immaterial. Any question can be made immaterial by subsuming all its answers under a common head.—William James, *Principles of Psychology*, 1842–1910.

Pulmonary Vascular Resistance in Man at Different Intravascular Distending Pressures Measured in a Case of Mitral Stenosis Complicated by Anomalous Pulmonary Venous Connection

By B. L. LENDRUM, M.D., AND A. M. LICHTMAN, M.D.

The factors capable of altering pulmonary vascular resistance in man have not been entirely clarified despite numerous studies. The authors have studied this problem in an unanesthetized human and demonstrated that one mechanism altering human pulmonary vascular resistance is change in venous pulmonary intravascular distending pressures.

MEAN vascular resistance in the pulmonary circulation is calculated from the blood flow and pressure measurements by means of the simple relationship

$$R = \frac{P}{F}$$

where P represents the pressure gradient between the pulmonary artery and the pulmonary vein, F, the blood flow per unit time, and R, the vascular resistance. For a given pressure gradient and flow rate, R will be determined, among other things, by the physical dimensions of the channels that the blood traverses. In a rigid hydraulic system this formula applies over a wide range of flow and pressure, and R remains constant. In the living subject, however, numerous mechanisms act on the vessels to change their caliber, hence R becomes a variable.

The effect of passive distention on the vascular resistance has been studied recently by several investigators on various animal preparations. Thus, Phillips, Brind, and Levy[1] found that for a constant pressure gradient between the femoral artery and vein, the flow in the denervated hind leg of the anesthetized dog increased with increasing intraluminal pressures. They concluded that the resistance dropped with increasing vascular distending pressure, leading to passive dilatation of the vessels.

Borst, McGregor, Whittenberger, and Berglund[2] demonstrated in dogs that the pulmonary vascular resistance progressively decreased as left atrial or pulmonary artery pressure rose, becoming relatively constant at left atrial pressures above 15 mm. Hg. The vessels subjected to high "distending pressures" behaved like rigid tubes, in that flow became more nearly linearly related to perfusion pressures (mean pulmonary artery pressure minus left atrial pressure).

Carlill and Duke[3] also showed in cats that increasing left atrial pressure to 15 cm. of saline decreased pulmonary vascular resistance and increased pulmonary blood volume. Further increase in left atrial pressure produced little additional change in pulmonary vascular resistance at constant flow. They found no change in vascular resistance following atropine, stellate ganglionectomy, or vagosympathetic nerve section in the neck. They concluded that the change in vascular resistance was due to passive distention of the vascular bed produced by increasing the left atrial pressures.

From the available animal experimental evidence it would thus appear that passive distention of a vascular bed by increasing intraluminal pressure is a mechanism that can effectively lower vascular resistance until maximal distention is achieved, at which point the blood vessel behavior approaches that of rigid tubes.

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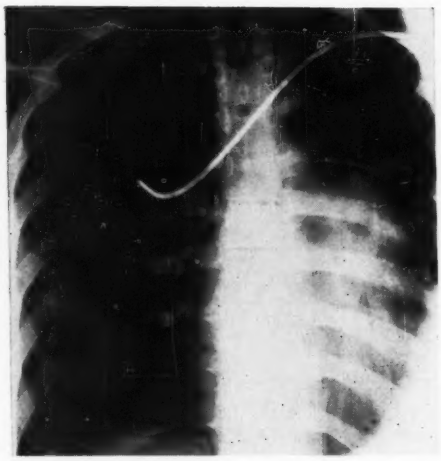

FIG. 1. Anteroposterior x-ray showing the cardiac catheter in the anomalous pulmonary vein, entered from the superior vena cava.

Sepulveda, Lukas, and Steinberg[4] reported studies on a case of partial anomalous pulmonary venous drainage into the left innominate vein in a patient with mitral stenosis. They found, according to their calculations, that the pulmonary vascular resistance in the anomalously draining left lung was higher than in the normally draining right lung. They offered no explanation for this difference in resistance, nor do they prove conclusively that the entire left lung drained to the right atrium, though this was assumed in the calculation of the vascular resistances.

Recently, we were also able to study the pulmonary vascular resistance in an unanesthetized patient with mitral stenosis and partial anomalous pulmonary venous connection to the superior vena cava (fig. 1). Two different venous distending pressures acted on the pulmonary vascular bed. Our studies suggest that passive (venous) distention of the human pulmonary vascular bed can lead to decreased vascular resistance, just as was found in the experimental animal studies.

CARDIAC CATHETERIZATION STUDY

The data obtained during cardiac catheterization of a 25-year-old woman are shown in table 1. Mitral commissurotomy was subsequently performed by Dr. Laurence Rubenstein, who reported a very tight mitral stenosis that barely admitted a fingertip.

Moderate right ventricular and pulmonary arterial hypertension was present at rest, 40/0 and 42/18 mm. Hg, respectively. Thus, the distending pressure on the pulmonary arterial side was abnormally high but acted uniformly throughout the lung.

On the pulmonary venous side there were 2 different levels of distending pressures acting on the lung vasculature. The mean pulmonary arterial wedge pressures obtained in 2 left pulmonary artery branches and in 2 of the most caudal branches of the right pulmonary artery to the portion of the right lung field just above the diaphragm was 24 mm. Hg $\pm$ 1 mm. (fig. 2). (These values not only checked each other very closely, but were the same as the pressure obtained by needle puncture of the left atrium at the time of mitral commissurotomy.) Two other mean pulmonary artery wedge pressures obtained in branches going to the right midlung field were found to be 10 mm. Hg (fig. 3). (This was very close to the value of 9 mm. Hg obtained with the catheter tip in an anomalous pulmonary vein draining from the right lung into the superior vena cava (fig. 4).) On withdrawing the catheter from all 6 of these wedge positions, the catheter was observed fluoroscopically to snap free suddenly like a cork popping out of a stoppered bottle. Coincident with the movement, the recorded pressures rose abruptly to similar levels in all instances, namely, to the level of the mean pulmonary artery pressure, 30 to 32 mm. Hg. The recorded curves associated with the higher value of 24 $\pm$ 1 mm. Hg showed the typical biphasic character usually obtained in the pulmonary artery wedge position in a patient with sinus rhythm (fig. 2).

Thus, it is apparent that some of the pulmonary blood flow drained in normal fashion to the left atrium, where the pressure was abnormally high and some of the pulmonary blood flow drained in abnormal fashion via an anomalous pulmonary vein that entered the superior vena cava (fig. 1) to the right atrium, where the pressure was normal.

The diagnostic series of blood samples revealed, as expected, a rise of 3 to 4 volumes per cent in oxygen content in the superior vena cava and right atrium above the value found in the left innominate vein. Further, the blood oxygen content in the inferior vena cava was 1 to 2 volumes per cent lower than that in the right atrium and superior vena cava, the reverse of the usual relationship in the absence of intracardiac shunts. An interatrial septal defect seems unlikely because of the widely differing magnitudes of the left atrial mean pressure, 24 mm. Hg (as measured indirectly by the pulmonary artery wedge pressure) and the right atrial mean pressure, 2 mm. Hg (as measured directly). The systemic arterial blood was 96.5 per cent saturated at rest and 94.2 per cent saturated on exercise, hence no significant right-to-left shunt was present.

The pulmonary and systemic blood flows and left-to-right shunt were calculated. The arteriove-

TABLE 1.—*Right Heart Catheterization Data before Operation*

	Oxygen content (vol. %)		Pressures (mm. Hg) systolic/diastolic (mean)	
	Rest	Exercise	Rest	Exercise
Inferior vena cava	13.4			
Superior vena cava	14.4			
	14.7			
Innominate vein	11.5			
Right atrium			(2)	(10)
High	15.9			
Mid	15.4			
Low	14.6			
Right ventricle			40/0	82/8
Low	14.4			
Mid	14.9			
High	14.6			
Main pulmonary artery	14.0	14.0	42/18 (32)	82/32
Right pulmonary artery	14.7		40/18 (30)	80/34 (50)
	15.0			
	15.5*			
Left pulmonary artery			40/20 (32)	
Pulmonary artery wedge				
Right lower lung	15.8		(24)	(37)
Right middle lung	15.8		(10)	
Left lung			(24)	
Anomalous pulmonary vein remote from SVC	16.5		(9)	
Anomalous pulmonary vein wedge			40/20 (28)	
Brachial artery			90/65	118/82
Content	17.5*	18.1		
Capacity	18.4	19.5		
Saturation	96.5%	94.2%		

	Rest	Exercise
Oxygen consumption		
(ml./min.)	178*	318
(ml./min./M.²)	118*	211
Systemic blood flow (L./min.)	3.6	
Pulmonic blood flow (L./min.)	6.6	7.8
Left-to-right shunt (L./min.)	3.0	
Cardiac index		
Systemic	2.4	
Pulmonic	4.4	5.1
Pulmonary vascular resistance (dynes-sec.-cm.$^{-5}$)		
Anomalously draining lung	559	
Normally draining lung	178	

* Simultaneous measurements.

nous difference used in calculating pulmonary flow was obtained by using the average oxygen content of all the pulmonary artery resting samples, 14.8 volumes per cent, rather than the single right pulmonary artery value of 15.5 volumes per cent obtained simultaneously with the brachial artery sample and oxygen consumption measurement. This was done because of the rather wide fluctuation in the oxygen content of the pulmonary arterial blood samples—which was attributed to stream-line flow. The arteriovenous difference used in calculation of systemic blood flow was obtained by using the average oxygen content of the inferior vena cava and left innominate vein samples.

The pulmonary blood flow was found to be 6.6 L. per minute and the systemic blood flow 3.6 L. per minute. The left to right shunt flow was 3.0 L. per minute. Thus, 45 per cent of the pulmonary flow

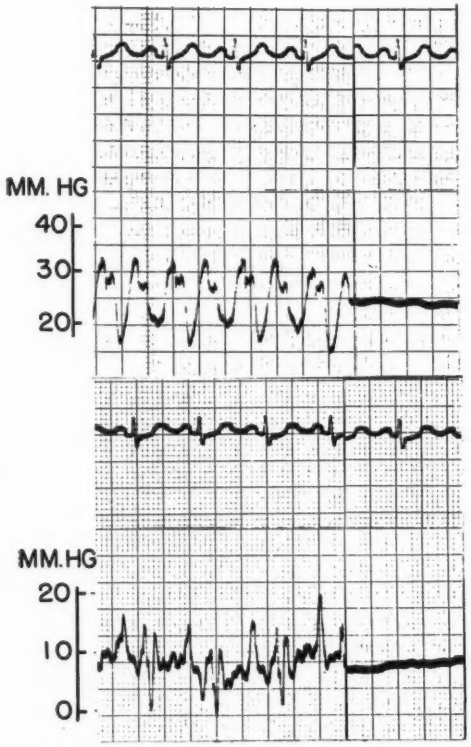

FIG. 2 *Top.* Pulmonary artery wedge pressure curves obtained with the catheter wedged in a left pulmonary artery branch. Mean pressure is 24 mm. Hg. Note typical biphasic curve.

FIG. 3 *Bottom.* Pulmonary artery wedge pressure curve obtained with the catheter wedged in a pulmonary artery branch going to the middle lobe of the right lung. Mean pressure is 10 mm. Hg.

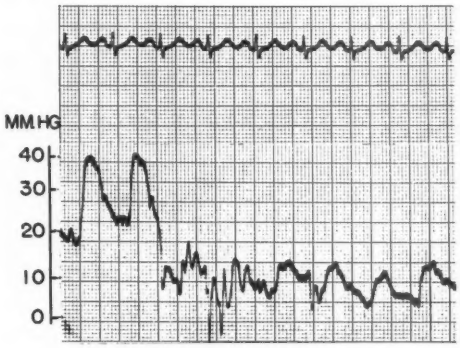

FIG. 4. Pressure curves obtained as the catheter was withdrawn from the wedged position in the anomalous pulmonary vein into the pulmonary vein.

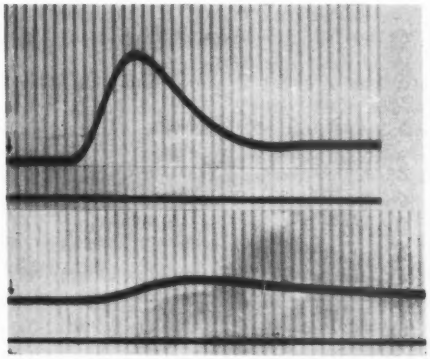

FIG. 5. Dye curves recorded using an ear oximeter; 25 mg. Evan's blue dye were injected into the right and left main pulmonary artery branches close to the main pulmonary artery. The upper curve was obtained by injection into the left main pulmonary artery and shows a normal contour. The lower curve was obtained by injection into the right main pulmonary artery and shows, by contrast, a flat contour and prolonged build-up and disappearance times, typical of a large degree of pulmonary recirculation. The arrows mark the time of injection. The time lines indicate intervals of 1 second.

was via the anomalous pathway to the right atrium and 55 per cent via the normal pathway to the left atrium.

The mean pressure gradient across the normally draining lung was 8 mm. Hg (mean pulmonary artery pressure minus mean left atrial pressure), and the mean pressure gradient across the anomalously draining lung was 21 mm. Hg (mean pulmonary artery pressure minus mean anomalous pulmonary vein pressure).

The pulmonary vascular resistance for each pathway was calculated. The resistance of the anomalously draining lung was found to be 559 dynes-sec.-cm.$^{-5}$ and that of the normal pathway 178 dynes-sec.-cm.$^{-5}$ Calculated resistances have meaning only for the total vascular bed or for known fractions thereof. To attempt to establish the proportion of the total pulmonary vascular bed draining via the 2 pathways, dye-dilution curves were used.

Evans blue dye was injected into the right and left pulmonary arteries and dye curves were obtained by means of an ear oximeter (fig. 5), as described by Swan, Burchell, and Wood.[5] The dye curve obtained from the left pulmonary artery was normal in contour and suggests neither right-to-left nor left-to-right shunts. It showed an arrival time of 6½ seconds, build-up time of 6½ seconds, and disappearance time of 10½ seconds. The curve obtained

from the right pulmonary artery was strikingly different in contour. The curve was much flatter and prolonged. The arrival time was approximately the same as in the left pulmonary artery, namely 7 seconds, the build-up time was longer, 12 seconds, and the disappearance time was likewise much longer, more than 27 seconds. (Measurement of the disappearance time is grossly inaccurate because of the flatness of the curve.) The right pulmonary artery dye curve was consistent with the anomaly found. The normal arrival time indicated that some blood flowing into the right lung went to the left atrium without recirculating through the lung. The amount of blood following this pathway was very small judging from the absence of a conspicuous peak in the early portion of the curve. The pathway to the left atrium on initial circulation through the lungs must have been through the lowermost portion of the right lung, where the mean pulmonary artery wedge pressure of 24 mm. Hg was obtained. The prolonged build-up time and disappearance time as well as the flattened contour of the curve are characteristic of large left-to-right shunts and pulmonary recirculation. The dye curve obtained from the right pulmonary artery suggested that most of the blood flowing into the right lung drained into the right atrium. Thus, the dye curves suggest that the entire left lung drained to the left atrium and that most of the right lung drained to the right atrium.

Discussion

The finding of a much higher vascular resistance in one part of a lung field than in another in the same patient raises some fundamental questions about the mechanism operating to vary pulmonary vascular resistance. Increased flow associated with long-standing pulmonary hypertension has been postulated to cause morphologic changes in lung vascular structure: muscular medial thickening and intimal proliferation of the pulmonary arterioles and small arteries.[6] Despite a systemic flow below normal in our patient, the blood flow was above normal through each lung and pulmonary hypertension was present. Our data suggest that the flow through each lung field was approxinately the same per unit volume of lung; from what is known of flows in other cases of anomalous pulmonary venous connection (see below) this was probably always so in this patient. Hence, it would seem unreasonable to assume that increased flow together with pulmonary arterial hypertension would selectively increase the vascular resistance in the anomalously draining lung. It is unfortunate that the state of the patient at surgery did not permit us to obtain a biopsy of the right middle lung; we are, therefore, unable to compare the morphology of the vasculature of the 2 differently draining lung fields. A biopsy of the left lung showed normal vascular structure.

One might postulate a variable constricting mechanism acting to a greater degree of the pulmonary vasculature in the anomalously draining lung to explain the apparent differences in vascular resistances found in the 2 lung fields. The site and mechanism by which such a mechanism might occur is unknown.

An alternative explanation is the purely mechanical action of *passive* vascular distention that was much greater in the lung vessels draining into the left atrium than in those draining into the superior vena cava. That increased intraluminal distending pressure results in decreased vascular resistance in the experimental animal is well documented.[1-3] There is no reason to suppose that this mechanism does not occur in man.

The pulmonary vascular resistance of the normally draining lung was roughly one third that of the anomalously draining lung. This might conceivably be due to the vascular bed of the normally draining lung being 3 times as large anatomically (i.e., containing 3 times the number of vascular channels) as the anomalously draining lung. If we assume equal vascularity throughout the lung and roughly equal volumes for the right and left lungs, this would mean that half the right lung would need to drain to the left atrium in order to explain the reduction in resistance found. Although we do not know the exact volumes of the lungs draining to each atrium, we do have some evidence on which to base estimates of relative size. The dye curve obtained by injecting dye into the right pulmonary artery showed much less dye going to the left atrium than to the right atrium on first circulation through the right lung. Hence, considerably less than half the right lung must drain to the left atrium. It therefore follows that disparity in size of vascular beds cannot entirely explain the differences in calculated vascular resistances found.

Catheterization data clearly demonstrated that 2 different intravascular distending venous

pressures acted on the lung vasculature in this patient. The pulmonary artery pressure was the same throughout, hence was not a factor involved. The pulmonary vein pressure of the anomalously draining lung was 9 mm. Hg, as opposed to 24 mm. Hg in the pulmonary veins of the lung segments draining into the left atrium—a significant difference. Moreover, the distending pressure of 9 mm. Hg is well below, and 24 mm. Hg is well above the critical value of 15 mm. Hg at which experimental evidence indicates that maximum distention is achieved.[2, 3] Thus, on this basis, the difference in distending pressure in our patient should have resulted in a considerable increase in the caliber of pulmonary vessels in the lung draining into the left atrium. It would seem to offer the best explanation for our finding of a decreased vascular resistance in the lung field draining into the higher pressure area of the left atrium.

The size of the calculated shunt correlates surprisingly well with the distribution of the blood flow through the lungs in uncomplicated cases of partial anomalous pulmonary venous connection studied and reported by Mankin and Burchell.[7] They concluded that the magnitude of recirculation is proportional to the number of lobes from which the blood is returned to the right side of the heart. This likewise has been found to hold in other cases of isolated partial anomalous pulmonary venous connection that we have studied.

Mankin and Burchell predicted that should mitral stenosis develop in a patient with partial anomalous pulmonary venous connection, the latter lesion would act as a sort of "safety valve" and protect the lungs from congestion whenever the left atrial and pulmonary capillary pressure rose, by providing a bypass to a region of lower pressure, namely, the right atrium. This, they predicted, would permit a greater proportion of the pulmonary blood to flow to the right atrium. Our data, however, do not support this premise. The additional lesion of mitral stenosis in our case and in the case of Sepulveda, Lukas, and Steinberg[4] apparently seemed to cause no radical redistribution of blood flow such as was predicted by Mankin and Burchell. In the case reported by Nichols, Woldow, and Goldberg,[8] where mitral stenosis and an anomalously connected pulmonary vein coexisted, the flow through the anomalously draining lung also was apparently not significantly changed by the presence of the mitral stenosis. (They published no data that permit calculation of the pressure gradients or size of the lung field draining anomalously.) They found at surgery mitral stenosis and an anomalous left superior pulmonary vein. This correlated well with their preoperative study that showed that 1.2 L. per minute flowed through the anomalously draining lung, while 2.5 L. per minute flowed through the normally draining lung; hence only one third of the pulmonary flow drained to the low pressure area, the right atrium.

Thus, instead of the anticipated facilitation of flow of blood through the lungs draining to lower pressure areas, which would tend to decrease systemic blood flow, a sort of compensatory mechanism acts to decrease the vascular resistance of the normal pathway and to maintain an adequate systemic circulation.

It is very likely that passive vascular distention explains, as Borst, McGregor, Whittenberger, and Berglund[2] have suggested, the occasional patient we have studied with tight mitral stenosis who is found to have normal pulmonary artery pressure and *decreased* pulmonary vascular resistance.

The same mechanism may operate to reduce pulmonary vascular resistance in early left ventricular failure of any etiology that elevates left atrial pressure sufficiently to cause passive distention of the pulmonary venous bed. Thus, normal flow would tend to be maintained without necessarily resulting in a markedly increased pulmonary arterial pressure.

Summary

Pulmonary vascular resistance was studied in a case of mitral stenosis complicated by partial anomalous pulmonary venous connection to the superior vena cava. Pulmonary hypertension and a markedly elevated left atrial pressure were found to be present.

Evidence is presented that suggests that the blood flow through all lung segments was approximately equal. The pressure gradient across

the anomalously draining lung was roughly 3 times that across the lung draining to the left atrium, yet the flow through each was approximately the same. The conclusion is drawn that the pulmonary vascular resistance in the lung draining to the left atrium is one third that in the lung draining to the superior vena cava. It is suggested that the decreased vascular resistance of the lung draining to the left atrium can, at least in part, be attributed to passive dilatation of the vessels by the high left atrial pressure.

Acknowledgment

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Summario in Interlinguia

Le resistentia pulmono-vascular esseva studiate in un caso de stenosis mitral complicate per partial connexion pulmono-venose al vena cave superior. Le studio esseva executate per medio de catheterisation dextero-cardiac. Esseva constatate le presentia de hypertension pulmonar e un marcate elevation del pression sinistro-atrial.

Es presentate datos que indica que le fluxo de sanguine in omne segmentos pulmonar esseva approximativemente equal. Le gradiente de pression a transverso le pulmona a drainage anormal esseva quasi 3 vices le gradiente a transverso le atrio sinistre, sed le fluxo in le duo esseva plus o minus identic. Es concludite que le resistentia pulmono-vascular in le pulmon a drainage verso le atrio sinistre es un tertio del correspondente resistentia in le pulmon a drainage verso le vena cave superior. Es formulate le interpretation que le reducite resistentia vascular del pulmona a drainage verso le atrio sinistre se explica al minus in parte per le dilatation passive del vasos sub le effecto del alte pression sinistro-atrial.

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CLINICAL PROGRESS

Current Concepts on the Management of Shock

By MAX H. WEIL, M.D., PH.D.

SHOCK is a descriptive term used by clinicians to denote a syndrome that is characterized by protracted prostration and hypotension and usually is accompanied by pallor, coldness and moistness of the skin, collapse of superficial veins, alteration of mental status, and suppression of the formation of urine. A voluminous literature reflects intense disagreement over the meaning and the significance of the term. Most of this, however, results from the use of a single name to describe a condition produced by many unrelated causes; occasion for disagreement disappears if the term shock is used within the limits of its definition—namely, to indicate the clinical state of the patient without specific implication as to the underlying cause.

"Vasomotor collapse" and "peripheral vascular failure" are frequently employed by authors to circumvent the dispute aroused by use of the term shock. These names are subject to the same misunderstanding and add hemodynamic implications that may be misleading. Shock simply refers to the presenting signs of the patient, and within this limit the term is valid and meaningful.

HEMODYNAMIC MECHANISMS IN SHOCK

In order to give a patient the advantage of rational and effective treatment, it is essential to determine in each case the specific cause of shock. Yet, at the same time, it is possible and helpful to think of a general mechanism that is involved. To illustrate the relationship between a specific mechanism and the general mechanism, the results of some recent investigative studies may be cited.

From Overwhelming Infection. The cause of shock that occurs during overwhelming infections due to gram-negative bacteria has been studied in laboratory dogs after intravenous injection of endotoxins derived from *Brucella melitensis* or *Escherichia coli*.[1-3] Within 1 minute following such an injection, arterial pressure falls sharply and portal venous pressure increases pronouncedly. The liver and intestines become engorged with blood, suggesting that the fall in arterial pressure and the elevation of the portal venous pressure result from pooling the blood in the splanchnic venous bed. Direct measurements of the change of weight of the liver and intestines indicate that large amounts of blood are pooled in these organs. Measurement of venous flow into the heart demonstrates that the volume of blood returned to the heart is correspondingly decreased. When the cardiac output is determined, a quantitatively similar decline is observed which is the direct cause of the sharp fall in arterial pressure. A secondary and late feature involves electrocardiographic evidence of myocardial ischemia. This is attributed to reduction in blood flow through the coronary arteries because of the sharp decline in arterial pressure. The resulting reduction in coronary flow, if sufficiently prolonged, leads to defective myocardial contractility. Thus cardiac output declines further and arterial pressure falls even lower. These hemodynamic features, beginning with the reduction in effective volume of circulating blood caused by pooling, are presented schematically in figure 1. It is apparent that 2 vicious circles are established. One is related to pooling and the other to coronary insufficiency. These factors may intensify and propagate the state of shock long after the initiating disturbance has taken place.

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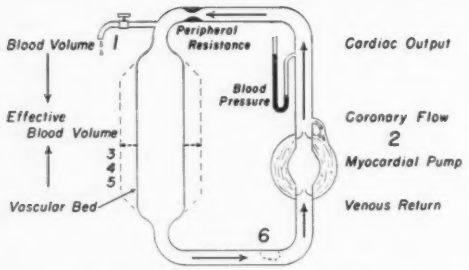

FIG. 1. A model of the circulatory system illustrating the relationship of clinical conditions to hemodynamic disturbances that may lead to shock. The 6 numbers in this figure refer to the 6 causes of shock listed in table 1.

TABLE 1.—*Classification of Specific Causes of Shock*

1. Hypovolemia
   Hemorrhage, dehydration, loss of protein
2. Cardiac failure
   Myocardial infarction, cardiac dysrhythmia
3. Hypersensitivity
   Anaphylaxis, reaction to drugs
4. Bacteremia
   Bacterial toxins (endotoxin)
5. Neurogenic factors
   Vasomotor paralysis, spinal shock, ganglionic blockade
6. Impediment to blood flow
   Pulmonary embolism, dissecting aneurysm

From Other Causes. The schema serves equally well as a general outline of the mechanism involved in the development of shock from various causes. Table 1 provides a tentative classification of the various types of shock encountered in clinical practice. Six different mechanisms are listed, and each of them may be related to the general mechanism indicated in the figure.

Hypovolemia results from hemorrhage, dehydration, loss of protein, or capillary leakage. When one third of total blood fluid is lost, a critical point is reached at which the volume of blood is no longer sufficient to fill the vascular bed.[4] The venous return and cardiac output are reduced to a level where compensatory vasoconstriction is insufficient to maintain the arterial pressure.

Cardiac failure may be caused by myocardial infarction or cardiac dysrhythmia. Failure of the cardiac pump reduces the cardiac output, sometimes severely enough to produce shock.[5, 6]

Hypersensitivity and, particularly, anaphylactic reactions are not completely understood. Present evidence, which is also based on studies in dogs, indicates that shock associated with these phenomena is mainly the result of sudden constriction of small hepatic veins followed by pooling of large quantities of blood in the portal venous bed, which leads to sudden reduction in venous return and cardiac output.[7] Thus the initial hemodynamic disturbance is similar to that of shock associated with bacteremia, already described in some detail.

In the absence of normal vasoconstrictive impulses that follow transection of the spinal cord, sympathectomy, administration of certain anesthetic agents, or drug-induced ganglionic blockade, normal neurogenic control of the caliber of blood vessels is lost. Vasodilatation may increase the capacity of the peripheral vascular bed, and especially the venous bed, to such an extent that the volume of blood is inadequate to fill this large space. The condition results in critical reduction of the venous return and cardiac output. Contrary to earlier concepts, loss of venomotor tone rather than decrease of arteriolar resistance appears to be the major defect in this type of shock.[8]

Finally, there is a type of shock that is brought about by physical obstruction of a main thoroughfare, so that the total blood flow is inadequate to maintain circulation, and therefore venous return and cardiac output are insufficient. The basic mechanism is analogous to the chain of effects from stepping on a garden hose. Pulmonary embolism and dissecting aneurysm are examples.

VASOPRESSOR AGENTS

The value of vasopressor agents in the treatment of some patients with shock has been widely recognized. Important considerations are the selection of a suitable pressor amine and the definition of the specific circumstances in which this type of drug is indicated.

The most potent vasopressor agents presently available are norepinephrine, or levarterenol (Levophed), and metaraminol (Aramine). Less potent drugs such as methoxamine (Vasoxyl), phenylephrine (Neosynephrine) and

mephentermine (Wyamine), which are available for the treatment of more transient forms of hypotension, will not be discussed here.

Effects of Levarterenol and Metaraminol. Levarterenol and metaraminol are useful allies in the treatment of shock caused by myocardial infarction, bacteremia, or hypersensitivity reactions, and usually provide a favorable effect against neurogenic shock. The beneficial effects in cardiogenic shock are related only in part to the improvement of coronary blood flow that follows elevation of the systemic blood pressure. Recent studies have shown that both these drugs have a direct beneficial effect on the myocardium, increasing the contractility of the myocardial fibers and thereby increasing cardiac output.[9, 10] In experiments with bacteremic shock in dogs, these drugs have been shown to remedy pooling by reducing obstruction to outflow from the splanchnic venous channels in which the large quantities of blood are pooled.[11] Similar considerations pertain to the use of pressor amines in the treatment of shock caused by hypersensitivity to drugs or foreign proteins. For immediate treatment of acute anaphylactic shock, which sometimes is accompanied by bronchoconstriction and increased resistance to the flow of blood through the lungs, epinephrine rather than levarterenol or metaraminol appears to be the agent of choice. For neurogenic hypotension, levarterenol and metaraminol are particularly apt and helpful, as they produce vasoconstriction by substituting the sympathomimetic action of these drugs for the vasoconstrictive action that is normally supplied by the sympathetic nervous system.

Seldom Indicated in Hypovolemia and Circulatory Block. The use of vasopressor drugs in the treatment of hypovolemic shock is only occasionally justified. Treatment in these patients requires replacement of the fluid that is lost. Blood, plasma, and electrolytic fluids are used in amounts that are calculated to re-establish normal volumes and concentrations in the intravascular space. The clinician will be guided in his selection of fluids by the history of fluid loss and also by laboratory study of the relative volumes and concentrations of blood cells, plasma, and electrolytes. In spite of its antigenicity, dextran possesses most of the attributes of an ideal plasma expander.[12] Used as a 6 per cent solution in isotonic saline, it is an expedient measure for treatment of hemorrhagic shock when whole blood or plasma is not immediately available. If shock persists after replacement of fluids, secondary pooling of blood and myocardial failure may be responsible in the vicious circles already described.[13, 14] This situation, which is referred to as "irreversible shock" by some authors, is not unlike that which exists in bacteremic shock, a feature that has been stressed by Fine and his coworkers.[15] In such instances, vasopressor agents may be helpful.

In the shock that results from physical impediment to blood flow, drugs that produce additional vasoconstriction are not ordinarily indicated.

Special Advantages of Metaraminol. Both levarterenol and metaraminol display the vasoconstrictive effects of epinephrine, but neither produces cardiac acceleration, stimulation of the central nervous system, or depression of the appetite.[16] Levarterenol has the unfortunate disadvantage of injuring tissues at the site of injection. Deep ulceration involving the skin and subcutaneous tissues has been a disturbing complication of its use and on occasion has required subsequent skin grafting and even amputation.[17, 18] In a recent report, Close and Kory[19] have indicated that local infiltration of adrenergic blocking agents such as tolazoline hydrochloride (Priscoline) or phentolamine hydrochloride (Regitine) is an effective means of preventing this complication. Other undesirable features of the prolonged use of levarterenol include the transiency of its action, which necessitates administration under constant nursing supervision, and the need for large quantities of fluid vehicle when this may be undesirable because of inadequate excretion of urine. Metaraminol, on the other hand, causes no local injury to tissue. It may be injected by intravenous, intramuscular, or subcutaneous routes without additional fluid vehicle, and it manifests a prolonged period of action.[16] In addition, metaraminol reportedly produces less constriction of the renal vessels than levarterenol for a dose that produces an equal

pressor response.[20] This may be of particular advantage in patients in whom renal complications of shock cause the output of urine to be inadequate, even though vasopressor agents are used to maintain blood pressure at a satisfactory level.

Following intravenous administration, the pressor effect of metaraminol becomes manifest in 1 to 2 minutes, is maximal in 5 minutes, and persists for 20 to 25 minutes. After intramuscular or subcutaneous administration, a pressor response is observable in 5 to 12 minutes and maximal at approximately 30 minutes. The action of the intramuscular dose persists for only 50 minutes, but the action of the subcutaneous dose continues for 90 minutes. For this reason, the subcutaneous route has been favored for the treatment of patients whenever possible.[16, 21]

Administration of Metaraminol. The treatment of a patient with profound shock may be started with a single intravenous injection of 3 to 10 mg. of metaraminol, which usually produces a prompt elevation of blood pressure. When the peripheral veins are collapsed, the agent may be injected directly into the femoral vein, whereupon the arterial pressure is elevated and the peripheral veins become more normally distended. An intravenous infusion can be started then without difficulty, and thus a time-consuming and traumatic cut-down procedure is avoided. In most patients, the blood pressure is well maintained by the subcutaneous administration of 3 to 25 mg. of metaraminol with injection repeated every ½ to 2 hours. In patients who respond poorly, a continuous intravenous infusion of metaraminol in a dosage up to 500 mg. per L. may be administered. After satisfactory control has been achieved, the subcutaneous route is preferable. With improvement, the pressor response to metaraminol becomes more intense and requires reduction in dosage. My colleagues and I have found it more practical to reduce the amount of injections rather than their frequency until use of the agent is entirely discontinued.

Review of Considerations. The use of vasopressor agents has been criticized on the ground that they reduce blood flow by excessive vasoconstriction.[22] Brunson, Eckman, and Campbell[23] have reported a high correlation between the administration of sympathomimetic amines to patients with shock and the finding of hepatic necrosis at postmortem examination. When these drugs are given to normotensive animals, vascular injury and extensive tissue damage may result.[24] Nevertheless, there is now abundant evidence that the correct use of these drugs in selected patients with profound shock is not accompanied by undue risk of damage to vital organs. In the presence of severe hypotension and the absence of hypovolemia or physical obstruction to blood flow, a point is reached beyond which administration of these agents results in an increase rather than a reduction in blood flow to vital organs.[25]

Influence of Acidosis on Vasopressor Response

Clinical observations have indicated repeatedly that patients with co-existent shock and acidosis respond poorly to vasopressor agents. In this connection Burget and Visscher[26] noted in 1927 that the response of the vascular system of the pithed cat could be altered by changing the pH of the blood, and that the response to epinephrine progressively increased as the pH was increased from 6.9 to 8.0. More recently, Page and Olmsted[27] demonstrated that the pressor action of epinephrine and levarterenol was diminished in dogs with respiratory acidosis. These facts suggested that similar considerations would pertain to patients with shock and acidosis.

Findings in Dogs. To test this idea, epinephrine, levarterenol, and metaraminol were administered to dogs under conditions of respiratory acidosis produced by the inhalation of 30 per cent carbon dioxide, and their reactions were contrasted to the response obtained when the pH was normal. The pressure and pH of arterial blood were recorded, and an electrocardiogram was obtained. It was found that in the presence of acidosis the pressor responses to each of the sympathomimetic drugs was somewhat diminished. Ventricular rhythm was not affected during acidosis, although marked dysrhythmia followed administration of these agents to dogs in the control

state. Pressor responses and cardiac dysrhythmias produced by epinephrine, norepinephrine, and metaraminol were also diminished in a similar group of test animals under conditions of metabolic acidosis produced by intravenous infusion of a dilute solution of hydrochloric acid.[28]

These coincident findings with respect to cardiac rhythm were interesting in themselves, and especially so in relation to the recent studies by Bellet, Wasserman, and Brody.[29] These authors reported that molar solution of sodium lactate increases the ventricular rate in patients with Stokes-Adams disease and proposed it for the treatment of this condition. It seems likely that the effectiveness of molar solutions of lactate is due, at least in part, to the increased activity of endogenous epinephrine and norepinephrine which is brought about by elevation of blood pH.

In order to separate the effect on cardiac rhythm from vasopressor effect, these same agents were administered to dogs subjected to total cardiac bypass. After the heart was excluded from the circulation, pressor responses under conditions of respiratory acidosis were uniformly much less than those obtained in the same animal after the pH was returned to or near normal levels.[28]

Effect of Molar Lactate in Patients. It was decided then to study at the bedside the value of correcting the acidosis by infusion of a molar solution of lactate. Six patients who had coexisting bacteremic shock and acidosis were treated. All six had received large doses of levarterenol or metaraminol before the studies, but in spite of this the mean arterial blood pressure was rarely more than 40 to 60 mm. Hg. The pH of arterial blood prior to treatment was as low as 7.06; following administration of 300 to 1,000 ml. of molar solution of sodium lactate, the pH was elevated to a maximal value of 7.51. During and after the intravenous administration of sodium lactate the blood pressure returned to near the normal range even though the infusion of vasopressor agents was decreased or discontinued. None of the patients survived for more than 7 days in spite of this treatment. However, it was significant that response to the vasopressor agents was restored by sodium lactate after the usual measures had failed.[30]

In view of the limited accumulation of clinical experience on the use of sodium lactate in the treatment of shock, conclusions regarding its value and the possible dangers involved in its use must await additional observations. For the present, it seems worthy of trial when all else has failed. Molar solution of sodium lactate is administered by continuous intravenous infusion at a rate of 5 ml. per Kg. of body weight per hour until a pH of approximately 7.50 is achieved. The average total dose in patients with moderately severe acidosis is believed to be approximately 10 ml. per Kg. of body weight.

Adrenocortical Hormones

Insufficiency and Shock. The ease with which shock may be precipitated in adrenalectomized animals is well documented. Their extreme susceptibility is diminished but not removed when these animals are sustained through treatment with saline. When they are optimally treated with adrenocortical hormones, normal susceptibility is re-established.[31] Similar considerations pertain to human patients with adrenocortical insufficiency. Thus the appearance of shock during an acute illness or following a minor injury may be the presenting sign of previously unrecognized Addison's disease. The administration of adrenal steroids is specific treatment. Clinicians recently have become aware of adrenocortical insufficiency in patients who have been treated with lengthy courses of cortisone or one of its analogs. Fatal circulatory failure has followed even minor surgical procedures on such patients when steroid therapy was withheld in the postoperative period.[32-34] Special precautions are necessary to assure preoperative and postoperative administration of these hormones, and such patients should be carefully observed and promptly treated if evidence of acute adrenal insufficiency becomes manifest.

These facts notwithstanding, there is no clear evidence that adrenal insufficiency usually is involved in the causation or progression of shock. Recent clinical reports have created doubt that adrenal insufficiency due to hemor-

rhage into the adrenal glands is a major factor in shock associated with acute meningococcal septicemia (Waterhouse-Friderichsen syndrome).[35, 36]

Use in Treatment of Shock. The corticosteroid drugs nevertheless have a definite place in the treatment of certain patients with shock. An important therapeutic action of these hormones is the suppression of inflammation, and particularly the suppression of the systemic reaction to inflammation. For this reason they have been employed in the treatment of patients with bacteremic shock or shock related to a severe hypersensitivity reaction, and, on occasion, surgical patients with shock related to extensive tissue injury.[37-39] By suppression of the manifestations of inflammation in a critically ill patient with high fever, rapid pulse, and hypotension, a period of grace is provided during which normal circulatory adjustment may be re-established and specific treatment instituted. These considerations apply only to instances of shock in which inflammation plays an important role.

Clinical and experimental evidence indicates that corticosteroids may potentiate the action of vasopressor agents.[40-42] The steroid drugs have been used with some success to re-establish or increase response to vasopressor agents in patients with shock.

Spink[39] has reviewed the indications for and the dangers involved in the use of corticotropin (ACTH) and the adrenal steroids in these critically ill patients. He has emphasized that the steroid drugs have profound metabolic effects that may be avoided by giving them for only brief periods. Although ACTH and the adrenal cortical hormones aggravate infection, the presence of infection should not deter from their use, provided that appropriate antibiotic therapy is given concomitantly.

For the treatment of these patients an initial intravenous injection of 50 to 100 mg. of hydrocortisone sodium succinate (Solu-cortef) is advised. Maintenance therapy for a period of from ½ to 5 days is provided by the continuous intravenous infusion of hydrocortisone (free alcohol) in proper dilution to supply 5 to 12 mg. per hour.

Indications for Use of Digitalis Glycosides and Atropine

Before vasopressor agents became available, digitalis was rather often employed in treatment of hypotensive states. It is apparent now, however, that digitalis is only occasionally of value and that it should be reserved for those instances in which specific indication exists—namely, congestive heart failure and cardiac dysrhythmia of supraventricular origin. Its use at other times may cause further decline in cardiac output and thereby intensify shock.

On occasion, severe hypotension may be caused in part by excessive vagal activity. This state actually may be worsened by the use of vasopressor agents, for they excite increased vagal activity with cardiac slowing.[16] Electrocardiographic study of patients in this condition may indicate bradycardia with lack of impulse formation at the sinus node. The administration of 0.6 mg. (.01 gr.) of atropine sulfate has provided gratifying improvement in pulse rate and arterial pressure in such instances. Fortunately only the vagotonic and not the vasopressor action of levarterenol and metaraminol is inhibited after such use of atropine. The effectiveness of the pressor amines is therefore not hampered. In selected instances atropine can be of remarkable benefit for the treatment of patients in shock.

Present Status of Chlorpromazine, Heparin, Hypothermia, and "Head-Down" Posture

Chlorpromazine hydrochloride is the principal ingredient of Laborit's lytic cocktail,[43] which has been widely discussed, particularly in popular magazines and newspapers, as the "hibernation" treatment of shock. Pretreatment with chlorpromazine reduces the mortality of animals following hemorrhage or injection of endotoxin.[44, 45] Despite its extensive use in France and Indochina and some enthusiastic reports from European centers, convincing proof of its clinical value in the treatment of patients with shock is lacking. Because chlorpromazine itself may markedly lower arterial pressure through a ganglionic-blocking effect, and because this drug reduces

the subsequent effectiveness of vasopressor agents, its use cannot be recommended at present.

On the basis of studies in dogs, development of "irreversibility" in shock has been attributed to the formation of minute thrombi that impede blood flow through vital capillary beds, especially in the lung.[46] Increased fibrinolytic activity of plasma is observed during shock and is interpreted by some workers as a compensatory response to such intravascular clotting.[47] The increased coagulability may be due to the release of thromboplastic agents in the blood stream from injured and ischemic tissue. Experimental proof of these explanations is incomplete. Griffith[48] stated that heparinization of patients with shock increases their chance for survival, presumably by the prevention of thrombosis in small vessels. As yet, however, the value of this mode of treatment is unconfirmed.

Favorable results have been achieved with the use of hypothermia in the treatment of shock. The principle of its use in this situation is similar to that of its use in cardiac surgery, namely to minimize the injury caused by inadequate blood flow to vital organs. Hypothermia has been reported to increase the survival of dogs subjected to hemorrhagic shock.[44] In treatment of 3 patients with bacteremic shock and high fever my colleagues at the University of Minnesota Hospitals and I have observed the use of a refrigerator blanket as described by Lewis, Ring, and Alden;[49] it was our impression that the clinical course of these patients was favorably influenced, although only 1 of them recovered. This mode of treatment may have promise but also requires further evaluation.

The head-down or so-called Trendelenburg's position is routinely used in many hospitals for patients with hypotension. This posture may be effective in restoring consciousness after a syncopal episode or during the initial period of shock that follows loss of blood or vasomotor paralysis. However, there is some doubt of its usefulness for prolonged periods after more specific treatment is started. Empirical observations in patients with protracted hypotension suggest that the head-down position may delay recovery, presumably by preventing return of normal postural vasomotor reflexes.[50, 51] For this reason as well as the comfort of the patient and the convenience of his nursing care, a 15-degree to 30-degree head-up position appears to be much more satisfactory, with reliance on more specific measures to maintain blood flow to the brain and other vital organs.

Summary

In the handling of a patient with shock it is essential to identify the underlying cause in order to plan rational treatment. On the basis of information presently available, the specific causes of shock have been classified into 6 groups: hypovolemia, cardiac failure, bacteremia, hypersensitivity, neurogenic factors, and obstruction to blood flow. Treatment was discussed with reference to these groups.

Vasopressor agents are helpful in most instances of shock related to cardiac failure, bacteremia, and hypersensitivity. They usually are contraindicated in shock due to vascular obstruction and in hypovolemic shock until optimal replacement of fluid has been achieved. Recent studies have indicated that metaraminol may be the pressor amine of choice because it is therapeutically effective, simple to administer, without risk of injury to skin and subcutaneous tissues, and available for injection without additional fluid (thus especially suitable for patients with renal failure).

Rigorous attention to the fluid and electrolyte state is of special importance. In the presence of acidosis, the response to vasopressor agents is greatly diminished. The use of molar solution of sodium lactate to re-establish this responsiveness has met with limited success and seems worthy of trial in selected cases.

Adrenocortical hormones may be of striking benefit in shock due to bacteremia or hypersensitivity when an overwhelming response to inflammation threatens life. These drugs may be used also to augment the effectiveness of vasopressor drugs. Relatively little risk is involved, provided that the periods of employment are short and that antibiotics are used concurrently.

The indications for the use of digitalis glyco-

sides in shock are the same as at other times, and their routine use is of no proved benefit and may be injurious. Atropine is of value when excessive vagal activity with bradycardia produces or complicates the hypotensive state.

Chlorpromazine is of no proved worth in the treatment of shock, and possible benefits achieved with anticoagulants are not established as yet. Preliminary observations suggest that hypothermia may be of some value. The head-down position provides only transient benefit in patients with shock, and its prolonged or routine use may delay recovery.

ACKNOWLEDGMENT

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ABSTRACTS

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ATHEROSCLEROSIS

Wilgram, G. F., Lewis, L. A., and Best, C. H.: Effect of Choline and Cholesterol on Lipoprotein Patterns of Rats. Circulation Research **5:** 111 (Jan.), 1957.

The relationship of cholesterol to vascular disease was investigated in the presence and absence of dietary choline. Dietary cholesterol leads to marked hyperlipemia (low-density lipoproteins and alpha lipoproteins) and hypercholesterolemia only in the presence of adequate choline. This indicates a close metabolic interdependence between both dietary elements.

AVIADO

Lipsky, S. R., Haavik, A., Hopper, C. L., and McDivitt, R. W.: The Biosynthesis of the Fatty Acids of the Plasma of Man. I. The Formation of Certain Chromatographically Separated Higher Fatty Acids of the Major Lipide Complexes from Acetate-1-C^{14}. J. Clin. Invest. **36:** 233 (Feb.), 1957.

Linoleic, oleic, palmitic, and stearic acids are the largest components of the sterol esters, phospholipids, and triglycerides. Most unsaturated acids were observed to be in the sterol esters while saturated acids were found mostly in triglycerides. Some of the fatty acids of phospholipides come partly from those of triglycerides. Transport of fatty acids in animals and man resides largely in the latter. After the use of acetate-1-C^{14}, most radioactivity appeared in palmitic fractions. Linoleic acid was not associated with radioactivity and this means absence of endogenous formation.

OPPENHEIMER

Creech, O., Jr., Jordan, G. L., Jr., and De Bakey, M. E.: The Effect of Chronic Hypercholesterolemia on Synthetic Aortic Substitutes. Surg., Gynec. & Obst. **104:** 385 (Apr.), 1957.

A previous study had shown that canine aortic homografts were more susceptible than the recipient aorta to atherosclerosis induced by chronic hypercholesterolemia. In the present similar study woven Orlon or Nylon aortic grafts were found to be uniformly resistant to atherosclerosis which, however, did develop in the recipient aorta in 10 of 16 dogs made hypothyroid with radioiodine and then hypercholesterolemic by cholesterol feeding for periods up to 13.5 months. In 3 dogs the induction at the proximal suture line of atheromas large enough to occlude the aorta suggests the importance of trauma as a pathogenic factor.

ROGERS

Wilkinson, C. F., Jr.: Drugs Other Than Anticoagulants in Treatment of Arteriosclerotic Heart Disease. J.A.M.A. **163:** 927 (March 16), 1957.

Atherosclerosis is viewed as beginning with an inherited subintimal defect, which under the influence of a number of secondary factors such as hypercholesteremia, diabetes mellitus and hypertension, first becomes inflamed, then incorporates lipid and finally forms a scar; calcification may occur producing a pearly plaque. Either the lipid or the pearly plaque may lead to occlusive disease, but only the former type of plaque seems reversible. In the author's experience, therapy with a number of drugs including sitosterols has been found ineffective in lowering the serum cholesterol value of normal individuals or of those with familial hypercholesterolemia. Estrogen therapy to the point of feminization has improved alpha and beta lipoprotein relationships in a high percentage of survivors of myocardial infarction, but such treatment is yet experimental inasmuch as it has not been shown to affect either morbidity or mortality from the disease. Familial hyperlipemia can usually be controlled by the consumption of a fat-free break-

fast and lunch, with unlimited fat in the evening meal.

ROGERS

Gottfried, S. P., Pope, R. H., Friedman, N. H., Akerson, I. B., and Tunison, J. R.: Studies of Serum Lipid and Turbidity in Atherosclerotic, Lipemic, and Normal Persons. Am. J. Clin. Path. **27:** 422 (April), 1957.

Specimens of serum from "normal," lipemic, and atherosclerotic men and women were incubated at 37.5 C. for 24 to 72 hours. Twenty-three of the 28 sera from atherosclerotic persons, 12 of the 15 from lipemic patients, and 4 of the 37 from "normal" persons were obviously turbid at the end of 72 hours. When a negative result was observed, and in instances where it was possible, a second test was performed with a sample of blood collected at a later date; if the second specimen of serum developed turbidity, it was classified as positive. Seven atherosclerotic patients who were nonambulatory, 3 lipemic patients who were ambulatory, and 11 "normal" men and women, ambulatory and nonambulatory, were fed a breakfast that had a high content of fats and cholesterol. Only 2 of the 7 atherosclerotic patients manifested a decrease in the levels of total lipid in serum collected 3½ hours after the meal, in contrast to such findings in the sera from 7 to 11 "normal" persons and all 3 of the lipemic patients. The effects of physical activity, and also the physiologic state of the persons, are regarded as possible explanations for the results observed in this study.

WENDKOS

Paronetto, F., Wang, C., and Adlersberg, D.: Lipoprotein Patterns by Starch Electrophoresis in Idiopathic Hyperlipemia and Hypercholesteremia. Circulation Research **5:** 288 (May), 1957.

Starch electrophoresis revealed marked increases of cholesterol and phospholipid (in the apha-2-lipoprotein fraction) of the serum from idiopathic hyperlipemia. Idiopathic hypercholesteremia showed an increase of these lipids in the beta-lipoprotein fraction. The cholesterol and phospholipid contents in the alpha-1-lipoprotein fractions were diminished in both metabolic errors. The consistent alpha-2-peak in idiopathic hyperlipemia suggested a causal relationship with the high concentration of serum triglyceride in this condition. Data in postprandial hyperlipemia showed that certain cholesterol and phospholipid molecules migrated with the mobility of the alpha-2-lipoprotein.

AVIADO

Strong, J. P., McGill, H. C., Jr., and Nyman, M. A.: Deposition of Lipid in Calf Aorta Maintained in vitro. Circulation Research **5:** 294 (May), 1957.

Perfused aorta showed preservation of basic histologic architecture of the aortic wall up to 12 days and the characteristic reaction of the aortic tissues to biologic stains. The biosynthesis of cholesterol, phospholipid, and fatty acids was confirmed by the finding of sudanophilic granules in the inner layers of the aortic wall, but there was a lag period of 24 to 48 hours between the chemical and the morphologic appearance of lipid. The simplest explanation for the lag period would be the necessary time for the synthesized lipids to aggregate into particles, but it is probable that more subtle influences of hormonal or enzymic nature are concerned. No structural change has been found in the perfused aorta that conforms to the classical description of atheroma in human beings. This fact is not at all surprising in view of the short period of the experiments, the species of animal used, and the absence of any lipophages in the perfusion system.

AVIADO

Wakerlin, G. E., Moss, W. G., and Kiely, J. P.: Effect of Experimental Renal Hypertension on Experimental Thiouracil-Cholesterol Atherosclerosis in Dogs. Circulation Research **5:** 426 (July), 1957.

There is clinical evidence indicating that hypertension accelerates the onset and accentuates the progress of atherosclerosis. Experimental proof is derived from dogs in which experimental renal hypertension accentuated the severity of thiouracil-cholesterol atherosclerosis. Sex of the animals had no significant effect on the incidence or severity of this experimental atherosclerosis, including coronary involvement.

AVIADO

Toor, M., Katchalsky, A.. Agmon, Jr., and Allalouf, D.: Serum-lipids and Atherosclerosis among Yemenite Immigrants in Israel. Lancet **1:** 1270 (June 22), 1957.

Israel's population is composed of immigrants from East and West. Not only is a higher atherosclerosis mortality rate found among immigrants from Western countries but also among Yemenites who immigrated over 20 years ago compared to those who arrived within the last 5 years. The nutritional status, serum cholesterol values, and incidence of atherosclerosis were investigated in recent and early Yemenite immigrants. Serum cholesterol and total lipid levels were significantly less in recent immigrants. The atherosclerosis mortality rate was 4 times higher in the early immigrants and in European Jews.

KURLAND

Malmros, H., and Wigand, G.: The Effect of Serum-cholesterol of Diets Containing Different Fats. Lancet **2:** 1 (July 6), 1957.

The effect on serum cholesterol of diets containing various fats was studied in experiments on healthy subjects each of whom received about 150 Gm. of fat daily supplying about 40 per cent of the calories. Corn oil and safflower-seed oil had a markedly depressing effect on the serum cholesterol, rape-seed

oil a moderate effect, olive oil a slight effect, and cocoanut fat no effect. Milk fat enhanced the cholesterol level. Experiments suggested that the cholesterol-depressing effect was related to the content of unsaturated fatty acids. Nineteen patients with essential hypercholesterolemia received pure corn oil and artificial milk, cheese, and ice cream made from it as well as a basic low-fat diet. Fourteen were treated for more than a year. The serum cholesterol fell within 2 weeks and in many patients it remained low (7 to 40 per cent below control). One patient was refractory.

KURLAND

Jones, R. J., Wissler, R. W., and Huffman, S.: Certain Dietary Effects on the Serum Cholesterol and Atherogenesis in the Rat. Arch. Path. **63:** 593 (June), 1957.

The role of various dietary ingredients in the pathogenesis of coronary atheromatous lesions in young albino rats was evaluated. A diet containing casein as the protein source, and lard and percomorph oil as the fat source over a 1-year period regularly resulted in coronary arterial atheromatous lesions. The incidence of lesions did not depend upon the presence of a high level of fat or cholesterol in the diet. The lesions were not influenced by lowering the level of protein or adding a supplement of a hypocholesteremic agent; nor were they reversed or prevented by alpha-tocopherol therapy, which improves nutrition and corrects the hypercholesteremia. Methionine supplementation alone exaggerated the hypercholesteremia and did not alter the frequency of lesions. The hypercholesteremia was reduced to control levels when *both* methionine and alpha-tocopherol were included in the experimental diet.

MAXWELL

Thomas, W. A., Konikov, N., O'Neal, R. M., and Taik Lee, K.: Saturated Versus Unsaturated Fats in Experimental Arteriosclerosis. Arch. Path. **63:** 571 (June), 1957.

The influence of saturated (butter, oleomargarine) and unsaturated (corn oil) dietary fats on thromboembolic-induced pulmonary arteriosclerosis in New Zealand white rabbits was compared with a control group fed an isocaloric amount of sucrose and water. Diets containing butter and oleomargarine markedly increased the extent of pulmonary arteriosclerosis, whereas similar quantities of corn oil had no such effect. Although the data would seem to indicate that the degree of saturation of the various fats may influence the lesions, other factors, such as essential fatty acid content, may be equally important.

MAXWELL

More, R. M., Movat, H. Z., and Haust, D. M.: Role of Mural Fibrin Thrombi of the Aorta in Genesis of Arteriosclerotic Plaques. Arch. Path. **63:** 612 (June), 1957.

Two postmortem cases are presented, both showing as incidental changes marked arteriosclerosis of the aorta characterized by the presence of multiple pearly white and white opaque plaques. Histologic examination showed the opaque plaques to consist of recent thrombus material, mostly fibrin. The pearly white plaques resembled older thrombi in various stages of organization, containing some areas of unorganized fibrinoid material, other areas of acid mucopolysaccharide-rich tissue with smooth muscle, capillaries, collagen, and elastic fibers. The authors believe that the microscopic changes seen in the opaque and pearly white plaques represent transitional stages in the organization of mural fibrin thrombi. The question as to whether fibrous plaques developing from fibrin thrombi represent an uncommon lesion or whether fibrin is one or possibly the only factor in the genesis of typical arteriosclerotic plaques is discussed but unanswered at this time.

MAXWELL

Wilens, S. L.: The Comparative Vascularity of Cutaneous Xanthomas and Atheromatous Plaques of Arteries. Am. J. M. Sc. **233:** 4 (Jan.), 1957.

Considerable histologic differences in the structural evolution of cutaneous xanthomas and arterial atheromatous plaques justify the interpretation that 2 totally unrelated processes are involved. However, if it is assumed that the major difference is in the initial vascularity of the 2 types of tissue involved, most of the diverse features can be explained. The lack of an adequate capillary circulation in the early stages of development of arterial plaques would account for the frequency of central necrosis, limited and peripherally located fibrosis, delayed resorption or replacement of lipid, and the high incidence of marked regressive changes. According to this view the absence of an intimal or subintimal capillary bed is responsible for many of the characteristic features of the atherosclerotic process. If such a circulation existed in the arterial wall, the atherosclerotic process would be greatly modified and perhaps would never develop in any form. The author bases his study on 58 cutaneous xanthomas encountered in the Surgical Pathology Laboratory of Bellevue Hospital over a period of about 15 years among a total of about 75,000 surgical specimens. Atherosclerotic lesions in all stages of development were available for study from routine necropsies.

HARRIS

Kaplan, S., Bossak, E. T., Wang. C. I., and Adlersberg, D.: Pregnancy Complicated by Idiopathic

Hyperlipemia and Idiopathic Hypercholesteremia. J. Mt. Sinai Hosp. **24:** 39 (Jan.–Feb.), 1957.

The authors report 2 pregnant patients with disturbances of lipid metabolism in whom successful delivery was achieved. The first patient was 25 years old and exhibited the chemical findings of idiopathic hyperlipemia without any external stigmata. Her pregnancy was complicated by attacks of acute pancreatitis in the last trimester. The second patient was 33 years old and showed not only the chemical findings of familial idiopathic hypercholesteremia but also xanthelasma and xanthoma tendinosum lesions. Early in her pregnancy she exhibited subjective and objective findings of myocardial infarction. At delivery, the cholesterol level of the newborn infants' blood was 148 mg. per 100 ml. (normal, 70 mg. per 100 ml.). In both patients serum lipid levels were higher during pregnancy than in the postpartum period. Restriction of dietary fat caused a lowering of lipid levels only in the first patient. The authors call attention to the normal rise in lipid levels during pregnancy.

ENSELBERG

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY, BALLISTOCARDIOGRAPHY, AND OTHER GRAPHIC TECHNICS

Bengtsson, E.: Working Capacity and Exercise Electrocardiograms in Convalescents after Acute Infectious Diseases with Cardiac Complications. Acta med. scandinav. **154:** 359 (June 9), 1956.

This study concerned 34 children and 34 young persons and adults who had been hospitalized with various infectious diseases. Observations of the working capacity and exercise electrocardiograms were made at the time of discharge and 1 month later. The working capacity of children was essentially the same as that of normal controls at both examinations. The working capacity of adults was reduced below normal at both the first and second exercise tests and more in women than in men. This decrease in working capacity seemed to be correlated with a decrease in heart volume as determined by roentgenographic study. The exercise electrocardiographic observations showed few significant differences from normal controls. Observations made with the patient in the upright position at the time of discharge from the hospital showed an average increase in heart rate of 20 beats per minute, only slight decreases in blood pressure, and electrocardiographic changes consisting of the appearance of high, peaked P waves, depression of the S-T segments and flattened, isoelectric or negative T waves or both. Electrocardiographic changes were more common in adults than in children, appearing in about one half of the former. The working capacity of a small series of trained athletes (3 cases) was much higher than that of normal convalescents when correlated with the heart volume.

ROSENBAUM

Černohorský, J.: A Vector Analysis of the W-P W Syndrome. Cardiologia **29:** 278 (No. 4), 1956.

A vectorial interpretation is presented of 22 patients with the Wolff-Parkinson-White syndrome based on the assumption that limb leads and standard leads may be regarded as manifestations of single instantaneous vectors. It was found that the forces responsible for the delta wave pointed in the frontal plane invariably in the direction of the QRS axis and in the horizontal plane always forward. In 4 patients the delta vector was perpendicular to V_2 with its positive portion projecting into the axis of V_6 and its negative portion into the negative part of the V_1 axis. The mean QRS vector pointed backwards in 7 patients and forward in 15. Left axis deviation was present in the frontal plane in 15 patients and in 11 there was a forward orientation of the mean QRS vectors. On the basis of this analysis the author concluded that the anomalous activation involved the posterior wall of the left ventricle or the ventricular septum and took place from the epicardium toward the endocardium. The usual left axis deviation in the frontal plane was determined, apart from the position of the heart and the relative weight of the 2 ventricles, by the localization and the extent of the ventricular muscle included in preexcitation.

PICK

Magistretti, M., and Fink, A.: Electrokymography in Congenital and Acquired Heart Disease. Relationships between the Phases of the Cardiac Cycle. Acta Cardiol. **11:** 435 (Fasc. 5), 1956.

The authors present hemodynamic observations based on a study of electrokymograms recorded simultaneously with the electrocardiogram in 60 patients with congenital and acquired heart disease. The material is divided into 2 groups according to the presence or absence of right heart failure. The data refer to the duration of the cycle, and its subdivisions under various circumstances and to changes in the dynamics of the 2 ventricles in some types of heart disease. The most important conclusions were as follows. In the absence of right heart failure a statistically significant inversed relationship exists between the right ventricular index and the isometric contraction. The isometric relaxation decreases as the ventricular output increases. Increase in pulmonary resistance (and mean pulmonary arterial pressure) leads to prolongation of the isometric contraction and to reduction of the ejection time of the right ventricle. In mitral stenosis isometric contraction of the right ventricle increases and isometric relaxation of both ventricles becomes shorter in proportion to the degree of stenosis; however, with development of right heart failure, isometric relaxation lengthens. In atrial septal

defects both hilar shadows and pulmonary arterial branches show hyperpulsation in contrast to pulmonic stenosis with a large pulmonary artery in which only the pulmonary trunks pulsate while the hilar shadows beat very slightly. Two peculiar pulsation patterns are described which characteristically may be found in aortic stenosis and in constrictive pericarditis.

PICK

Izak, G., Braun, K., and Mazri, S.: Esophageal Piezocardiogram in Mitral Valvular Disease. Cardiologia **29:** 291 (No. 4), 1956.

Atrial pressure curves were recorded via a balloon inserted into the esophagus in 11 normal patients, 16 patients with mitral stenosis, 11 with mitral insufficiency, and 4 with combined mitral lesions. In patients with sinus rhythm the tracing showed a constant pattern consisting of 3 upright waves, termed I, II, and III. In atrial fibrillation wave I was absent. In 8 patients the records were compared with direct left atrial pressure recordings obtained during surgery and a striking similarity between the 2 types of curves could be demonstrated. A statistical evaluation of the data obtained under the various circumstances revealed that neither the shape nor the amplitude of the different waves was of value in the differentiation of mitral stenosis and mitral insufficiency. However, the measurements of the distances between the waves appeared to be of some diagnostic importance in that in some patients with mitral insufficiency wave III reached its peak earlier in systole than in normal individuals and in patients with mitral stenosis.

PICK

Wilson, A. B. K., Fothergill, L., and Taylor, S.: Some Applications of a New Electronic Stethoscope. Lancet **2:** 1027 (Nov. 17), 1956.

The clinical use of an electronic stethoscope described by Taylor and Fothergill (Lancet **1:** 1050, 1956) is reviewed. Aside from its use by deaf physicians, application to the fetal heart sounds and to ausculation of patients in a "cabinet respirator" was particularly noteworthy.

MCKUSICK

Wilson, A. B. K., and Fothergill, L.: A Recording Sphygmomanometer. Lancet **2:** 1029 (Nov. 17), 1956.

Using an amplifying electronic stethoscope and a recorder the Korotkoff sounds record themselves on a direct-written record during deflation of a blood pressure cuff. Arrangement for automatic inflation of the cuff is in development.

MCKUSICK

Sigal, A. M.: The Mechanism and Clinical Significance of the Electrocardiographic Syndrome Showing Shortening of P-Q Accompanied by Changes in the QRS Complex (Wolff-Parkinson-White Syndrome). Klin. med. **345:** 52 (May), 1956.

A patient with mitral stenosis showed this syndrome, accompanied by episodes of paroxysmal tachycardia at the rate of 200, with every second ventricular complex containing inverted P waves and S-T segments in leads II and III; death occurred in 1 of these episodes. The syndrome was explained by spasm of the branch of the posterior coronary artery that supplies the A-V node (causing accelerated conduction and nodal tachycardia) and the posterior left bundle branch (causing the anomaly of QRS).

LEPESCHKIN

Aixala Alvarez, R., Muñiz Sotolongo, J. C., Sanchez, G. A., Fojo Echevarria, P., Triay, R., and Illanusa, J.: The Electrocardiogram in Experimental Cardiac Infarction. Rev. Cubana Cardiol. **17:** 23 (March), 1956.

In 15 dogs the electrocardiographic changes produced by temporary or permanent ligation of some of the branches of the coronary arteries were studied. Ligation of the posterior descending branch caused elevation of the S-T segment in lead III, which disappeared within 6 seconds after release of the ligature. Permanent ligation produced deep Q waves in leads II and III, which were especially pronounced in supplementary left dorsal leads. Ligation of the anterior septal artery led to depression of the S-T segment in aV_F, and elevation in leads aV_R and aV_L, while additional ligation of the anterior descending artery caused elevation of the S-T segment and T wave in aV_F. The syndrome of Wolff-Parkinson-White, which was observed to appear in several clinical cases of infarction, did not appear in experimental infarction.

LEPESCHKIN

Horsters, H. and Radel, J.: Radiocardiographic Measurements in the Pulmonary Circulation. A Contribution to the Shunt Problem. Arch. Kreislaufforsch. **24:** 204 (Aug.), 1956.

In animal experiments it was found that only radioactive sodium (11^{NA24}) and phosphorus (15^{P32}) can be used harmlessly for circulatory studies. In 69 patients 1 ml. of a sodium chloride solution containing 25 μC. of radioactivity was injected into the right cubital vein and the radioactivity curve in different parts of the body was recorded automatically. In normal persons the delay in radioactivity at the aortic arch, compared to that at the right atrium, was less than 3 seconds; this delay corresponds to the circulation time through the lungs. In patients with impaired pulmonary circulation this interval was prolonged. The presence of pulmonary shunts is characterized by an early and gradual rise of radioactivity at the aortic arch; these shunts show considerable activity even at rest

in the recumbent position, and in some cases result in a minimal pulmonary circulation time of only 0.5 to 1 second. The shunts may have the biological significance of preventing the oxidation of certain enzymes or hormones.

LEPESCHKIN

Ivanov, A. A. and Soboleva, A. V.: Late Electrocardiographic Effects of Heart Wounds. Klin. Med. (Moscow) **34:** 50 (Oct.), 1956.

Of 68 persons with foreign bodies that had remained 7 to 12 years in the heart, 37 had slight T-wave changes while 31 had normal electrocardiograms; many of these showed abnormalities after exercise. Among 12 similar patients who had the foreign bodies removed, only 1 showed a normal electrocardiogram. The T wave usually showed deep inversion in lead III although the foreign bodies had been removed from the anterior wall of the left ventricle in all patients. Abnormal Q waves did not appear, and this allowed differentiation from the pattern of myocardial infarction.

LEPESCHKIN

Ivanov, G. K.: Universal Calipers for Measuring Electrocardiographic Values. Klin. Med. (Moscow) **34:** 74 (Oct.), 1956.

The calipers are X-shaped, and allow threefold to fourfold magnification of small values. The values can be read directly in millivolts or seconds, as 2 sliding scales allow accurate adjustment for the actual sensitivity or paper speed.

LEPESCHKIN

Mozen, H. E., Katzman, R., and Martin, J. W.: Successful Defibrillation of Heart. Resuscitative Procedure Started on Medical Ward and Completed in Operating Room. J.A.M.A. **162:** 111 (Sept. 8), 1956.

This is a report of a 51-year-old woman with rheumatic heart disease, mitral insufficiency, and left ventricular enlargement, who developed ventricular fibrillation in spite of medical management. This occurred while an electrocardiogram was being taken. As a matter of last resort the chest was opened rapidly and manual compression of the heart was started approximately 2½ minutes after the onset of fibrillation. Mouth to mouth breathing was used for 15 minutes, then the lungs were inflated with 100 per cent oxygen through a tight fitting face mask. The patient was taken to the operating room and defibrillation was carried out with application of a single electric shock done through the intact pericardium. In the meantime the heart beat was maintained by manual massage. Five weeks later the patient was discharged out of the hospital without brain damage and with a regular sinus rhythm.

KITCHELL

Bishop, L. H., Jr., Estes, E. H., Jr., and McIntosh, H. D.: The Electrocardiogram as a Safeguard in Pericardiocentesis. J.A.M.A. **162:** 264 (Sept. 22), 1956.

Damage to the myocardium during pericardial paracentesis has occasionally been severe enough to result in pericardial tamponade and death. Animal experiments have shown that contact of the tip of the needle with the myocardium can be detected electrocardiographically if the needle is connected with the electrocardiograph in such a way as to constitute an exploring electrode with the machine set for the chest leads. Myocardial contact was indicated by elevation of the S-T or P-R segment, depending on whether ventricle or atrium was touched. This technic has been used by the authors in 40 patients requiring pericardial paracentesis. All were performed without complications. It is believed that the electrocardiogram is an additional safeguard in cases of pericardiocentesis, serving as an indication of the contact of the needle with the myocardium.

KITCHELL

Fields, T., Kaplan, E., Abrams, B., Simpson, R., Gordon, A., and Kenski, J.: Cardiac Monitor for Surgery and Resuscitation. J.A.M.A. **162:** 559 (Oct. 6), 1956.

Cardiac arrest, ventricular fibrillation, and profound shock demand immediate diagnosis and treatment. The apparatus described is a portable battery-powered electronic device for monitoring the electric impulse of the heart. The amplifier is a multistage transistor circuit that feeds a milliammeter and a headphone. Under normal conditions, in cardiac arrest, shock or peripheral vascular collapse, and in ventricular fibrillation, the monitor gives a characteristic diagnostic response.

KITCHELL

Frau, G. and Agostoni, A.: The Physiopathology of the Node of the Coronary Sulcus. Experimental and Clinical Study. Folia Cardiol. **15:** 177 (Apr.), 1956.

The anatomic and experimental investigations on the coronary sinus rhythm are reviewed. It is pointed out that the very existence of a node of specialized myocardial tissue located in the coronary sulcus is denied by some authorities; and that the electrocardiographic characteristics of systoles originated in this area are not well defined. In experiments in 25 dogs isolated ectopic beats or the shifting of the pacemaker to the "node of the coronary sulcus" were obtained either by depressing the chronotropism of the normal pacemaker or by stimulating the region of the coronary sinus. Two types of electrocardiographic changes were described: if the stimulus originating in the coronary sulcus spread to the atrial myocardium by way of the sinoatrial node, the contour of the P wave was only slightly modified; if the stimulus propagated directly to the atrial musculature, the P wave was characteristically

inverted in L_2 and L_3; the duration of the P-QR interval was normal or only slightly shortened: this finding differentiated this mechanism from the upper atrioventricular node rhythm. Observations were reported of electrocardiograms of 64 patients showing the typical pattern of "coronary sulcus" rhythm (53 patients) or extrasystoles (11 patients). The statistical incidence of this abnormality, its pathogenesis, and its pathologic or functional basis were presented; it was concluded that this finding per se had no definite prognostic implication.

CALABRESI

Bugaro, L., Dalla Volta, S., and De Castro, B., Considerations Regarding Right Branch Block Occurring in Cardiac Catheterization. Folia Cardiol. **15:** 275 (June), 1956.

One observation of right bundle-branch block, persistent for about 4 hours, and 2 other cases of transitory prolongation of QRS during cardiac catheterization are reported. The mechanism of these changes is interpreted in the light of the theory of Segers of the peripheral origin of some of the abnormalities characteristic of intraventricular conduction defects.

CALABRESI

Montemagno, F., Pagano, R., and Vitacca, L.: The Normal Electrocardiogram in a Dog. Folia Cardiol. **15:** 311 (June), 1956.

The electrocardiograms of 100 normal dogs, in the standard and unipolar limb leads and in 6 precordial leads, have been examined. The results of the measurements of the intervals and of single deflections are reported and compared with similar, more limited, studies of others; statistical analysis of some variables is given. It is concluded that the range of variation of the normal deflections is very large; that a right axis deviation in the frontal plane is frequent; and that respiratory arrhythmia is common in the dog.

CALABRESI

Yuceoglu, Y. Z., Richman, B., and Kisch, B.: The Influence of Respiration on the Ballistocardiogram in Animal Experiments. Exper. Med. & Surg. **13:** 243 (# 3), 1955.

In rabbits of large size, ballistocardiograms could be obtained of the action of the heart. Similar tracings were made by the respiratory movements of the animals. The findings of respiratory ballistocardiographic like waves in the rabbit, which occasionally showed all the waves usually seen in the human ballistocardiogram, warranted a report on these findings. It may, therefore, be rather difficult to accept certain physiologic factors used for the explanation of the HIJK waves as satisfactory, in view of the fact that the same waves can be produced by the movement of the body, due to respiratory movements of the animal. These movements, of course, do not correspond to the movements of the blood stream, which are supposed to be the main factors producing the HIJK waves in the ballistocardiogram. The similarity between the respiratory ballistocardiographic-like tracings of the rabbit and the cardiac ballistocardiogram of man should make us cautious in the interpretation of each wave before further exact quantitative experimental investigation is done.

BERNSTEIN

Venturi, V. M.: Unipolar Electrocardiograms of Isolated Rabbit's Hearts Treated with K-Strophanthoside (Strophoside). Acta pharmacol. et toxicol. **12:** 213 (fasc. 3), 1956.

Unipolar electrocardiograms recorded from isolated rabbit hearts showed changes after strophanthoside similar to those reported in isolated frog and intact cat hearts. A shortening of electric systole was confirmed as the commonest effect. The S-T interval was progressively shortened until a fusion between the QRS complex and the T wave could be seen, reaching biphasism in a preterminal phase before the onset of fibrillation.

AVIADO

ENDOCARDITIS, MYOCARDITIS, AND PERICARDITIS

Hill, R. W., Foulk, W. T., Butt, H. R., and Stauffer, M. H.: Chronic Constrictive Pericarditis Simulating Primary Hepatic Disease. Proc. Staff Meet., Mayo Clin. **31:** 627 (Nov. 28), 1956.

Chronic constrictive pericarditis may at times be confused with decompensated cirrhosis of the liver. Sixteen patients with chronic constrictive pericarditis in whom hepatic disease was simulated were reviewed. Hepatomegaly and ascites were the most frequent clinical findings. In 15 patients measurement showed elevation of venous pressure in an antecubital vein. This finding suggested the need for thoracic flouroscopy and electrocardiographic studies that led to the correct diagnosis. Tests of liver function with abnormalities resulting from hepatic congestion associated with chronic constrictive pericarditis may lend support to the diagnosis of primary disease of the liver. Normal concentrations of albumin in the serum in the presence of massive ascites should suggest that portal cirrhosis may not be the etiologic factor. The finding of ascites unassociated with peripheral edema and a relatively high value for protein in the ascitic fluid may also be helpful. Biopsy of the liver that discloses normal hepatic tissue in a patient with hepatomegaly and ascites should suggest the need for further definitive study to exclude the possibility of chronic constrictive pericarditis.

SIMON

Hepper, N. G. G., Burchell, H. B., and Edwards, J. E.: Cardiac Clinics. CXLVI. Mitral Insufficiency in

Healed, Unrecognized Bacterial Endocarditis. Proc. Staff Meet., Mayo Clin. **31:** 659 (Dec. 12), 1956.

A patient in whom mitral insufficiency caused by rupture of the chordae tendineae contributed to cardiac failure is presented. The lesions found on histologic examination were not unlike those seen in known cases of healed bacterial endocarditis. Before the chemotherapeutic and antibiotic era, spontaneous healing of subacute bacterial endocarditis was considered rare. It is logical to assume that with the widespread use of antibiotics in cases of febrile illness without diagnosis, the number of cases of unrecognized healed subacute bacterial endocarditis will be greater than in the period before the use of antibiotics. Healed bacterial endocarditis is a condition to be considered in the differential diagnosis of mitral insufficiency.

SIMON

Kaipainen, W. J. and Seppälä, K.: Endocarditis Lenta. A Review of 118 Patients Treated during the Ten-Year Period, 1945 to 1954. Acta med. scandinav. **155:** 71 (June 30), 1956.

A series of 118 patients with endocarditis lenta were treated. The blood cultures were positive in 42 patients and negative in 76 patients. Rheumatic heart disease was present in 63 per cent of the cases, congenital heart disease in 8 per cent and in the remainder the etiology of the heart disease was uncertain. In 13 of these latter patients the serologic test for syphilis was positive. The causative organisms in the 42 cases in which cultures were positive were *Streptococcus viridans* (60 per cent), *Streptococcus non-hemolyticus* (7 per cent), *Streptococcus faecalis* (17 per cent), *Staphylococcus aureus* (10 per cent), *Diplococcus pneumoniae* (2 per cent), *Gaffkya tetragena* (2 per cent) and *Salmonella enteritidis* Dublin (2 per cent).

Of 18 patients who received sulfonamide treatment or no antibacterial therapy, all died within 6 months. Of 39 patients who received penicillin in a total dosage of less than 15 million units, only 20 per cent lived 6 months and only 10 per cent were alive after 12 months. There were 21 patients who received more than 15 million units of penicillin and 38 who received penicillin in combination with other antibiotics; over 66 per cent of these patients were alive after 6 months and death thereafter was usually due to cardiovascular causes other than the infection. The relatively low incidence of positive blood cultures in this series (36 per cent) is attributed to (a) taking blood cultures during or immediately after antibiotic treatment, (b) too few blood samples, (c) poor sampling technic, or (d) defective blood culture technic. The authors believe that a patient with suspected endocarditis lenta should not be left untreated even though the blood culture is negative.

ROSENBAUM

Gellman, D. D., and Silberstein, K.: Perforation of Peptic Ulcer of the Œsophagus into the Pericardial Cavity. Report of a Case. Brit. M. J. **2:** 1413 (Dec. 15), 1956.

A 63-year-old man with a previous history of duodenal ulcer and "sliding" diaphragmatic hernia was awakened from sleep with severe retrosternal pain and became deeply shocked. There was heard a peculiar precordial murmur that could not be separated from the heart beat. "One had the impression that liquid was rushing through a narrow opening, the sound being comparable to that of water passing through a narrow gorge." Death occurred 21 hours after the onset of pain. The autopsy findings are outlined in the title. The case is similar in some respects to that reported by Parkes (Trans. path. Soc. London **2:** 40, 1849) of a 19-year-old sword swallower who some hours before death developed a "friction sound both diastolic and systolic . . . mixed with . . . a peculiar kind of metallic rhonchus carried up to the top of the sternum." "The diagnostic clue . . . was the peculiar murmur . . . the significance of which was not appreciated at the time. If it had been, the question of surgical intervention and pericardial toilet would have had to be considered."

MCKUSICK

Angela, G, and Angela-Artino, G.: Muscular, Pleural and Pericardial Changes in Guinea Pigs Infected by Coxiella burneti. Arch. sc. med. **102:** 158 (Aug.), 1956.

Guinea pigs were infected with *Coxiella burneti*, Bangui strain, by intraperitoneal inoculation; the animals were sacrificed 7 to 14 days after inoculation. In 3, out of 10, peculiar granulomatous pericardial foci were found; 4 animals showed pleural foci of inflammation. These lesions, which were described in some detail, were found in animals who also have typical splenic, pulmonary, and also myocardial changes. Other localizations in the skeletal muscles, especially in the diaphragm and in the intercostal muscles, were also illustrated.

CALABRESI

Spodick, D. H. Tuberculous Pericarditis. Arch. Int. Med. **98:** 737 (Dec.), 1956.

A review of the literature is highly suggestive of the not infrequent occurrence of tuberculous pericarditis, first described 104 years ago. This remains a serious lesion, difficult to diagnose and often symptomatically dormant despite the presence of characteristic massive effusions. Therapeutic success is not yet assured, despite the hopeful preliminary results with chemotherapeutic agents. Certain factors continue to influence prognosis with or without treatment; these include mode of onset, age, and ease of bacteriologic proof of etiology. Two cases, fairly typical of the developmental possibilities of

the acute lesion, are presented and related to the ensuing discussion. An understanding of the altered dynamics and pathophysiology of pericarditis and cardiac tamponade is emphasized as a key factor in the clinical management of this disease.

BERNSTEIN

HYPERTENSION

Oyen, I. H.: Mechanism of Early and Chronic Experimental Renal Hypertension as Tested by CCK-179. Am. J. Physiol. **186:** 161 (July), 1956.

A combination of dihydrogenated ergot alkaloids is referred to as CCK-179. This agent lowers blood pressure slightly, produces a moderate decrease in glomerular filtration rate but a marked reduction in renal plasma flow in normal control dogs. With repeated use the renal effects become more pronounced. Goldblatt hypertensive dogs were observed to have a reduction in blood pressure toward normal when this drug was used. At first the renal effects were like those seen in control animals but with time became progressively less. The possible role of increased sympathetic activity in maintaining increased peripheral resistance during chronic experimental renal hypertension is stressed.

OPPENHEIMER

Litchfield, J. W., and Peart, W. S.: Phaeochromocytoma with Normal Excretion of Adrenaline and Noradrenaline. Lancet **2:** 1283 (Dec. 22), 1956.

A 39-year-old man gave a 6-year history of paroxysms typical of pheochromocytoma. His resting blood pressure was normal but he was observed during numerous attacks when his blood pressure rose to 200/120 mm. Hg and characteristic accessory signs appeared. Histamine induced an attack. Presacral retroperitoneal pneumography with tomography revealed a probable tumor in or near the left adrenal. The urine from 3 separate 24-hour periods during each of which an attack occurred was assayed biologically for epinephrine and norepinephrine. The values were always within normal limits. On 3 occasions urine was collected after an attack and the results compared with urine collected in periods of similar duration with attacks. Twice there was no increased excretion; once there was a mild increase associated with a diuresis. The effects of infusion of epinephrine-norepinephrine solutions in a 1:2 ratio were tested. An attack like the spontaneous ones occurred, the only difference being that there was bradycardia not tachycardia as in the attacks. This suggested normal sensitivity on the part of the patient and a larger proportion of epinephrine in the secretion of the tumor than in the infused mixture. At operation a tumor weighing 10 Gms. was found near the left adrenal gland. It contained epinephrine 10 mg. per Gm. of wet weight and norepinephrine 4.25 mg. per Gm. of wet weight. Postoperative assays of urine gave results essentially the same as preoperatively. These results indicate that the urine tests are not infallible. This is theoretically to be expected because only a small percentage of the total epinephrine and norepinephrine is excreted in the urine, and the normal excretion varies widely, making it possible to have a tenfold increase in excretion without exceeding the upper limit of normal.

McKUSICK

Wells, C. A.: The Surgery of Hypertension: A Five-year Follow-up. Scottish M. J. **1:** 245 (Aug.), 1956.

The results of thoracolumbar sympathectomy performed over 5 years previously in 102 patients with essential hypertension are reviewed. The results in this series from Liverpool were essentially identical to those reported by Smithwick in a series approximately 3 times as large. Benefit was particularly striking in the Keith-Wagener group IV.

McKUSICK

Bekaert, J.: Influence of Neurogenic Hypertension on Adrenal Cortical Function. Exper. Med. & Surg. **13:** 304 (#4), 1955.

When neurogenic hypertension was produced in 4 dogs following bilateral extirpation of the carotid sinuses and section of the depressor nerves, a prolonged decrease of the blood eosinophils appeared. This decrease still occurred when the hypertension was produced in 5 animals which had been previously demedullated (operative removal of the adrenal medulla). This neurogenic hypertension was accompanied by a slight decrease in the concentration of plasma potassium; whereas, the plasma of sodium, remained almost unchanged. The onset of the neurogenic hypertension was followed by a definite but brief increase in the urinary excretion of corticoids.

MAXWELL

Magakian, G. O., Miminoshvili, D. I., and Kokaia, G. J.: Experimental Studies on the Pathogenesis of Hypertension and Coronary Insufficiency. Klin. Med. **34:** 30 (July), 1956.

The average blood pressure of 300 monkeys was 115–135/65–85, mm. Hg. Six had transient and 14 stable hypertension, and 26 showed electrocardiographic signs of "coronary insufficiency." These disturbances were attributed to neurosis resulting from conflicts of captivity. Monkeys continually subjected to conflicting stimuli (e.g., food and pain) for many years developed hypertension, sometimes preceded by hypotension, extrasystoles and inverted T waves in leads I, II, and III. In some cases the T-wave changes became normal after nitroglycerin. One monkey who died showed apical myocardial infarction with normal coronary arteries. In another monkey inversion of the T wave in leads II and III appeared only when it was falling asleep or waking up, but not in deep sleep or while it was awake.

LEPESCHKIN

Furbetta, D., Bufalari, A., and Santucci, F.: The Behavior of the U Wave of the Electrocardiogram in Arterial Hypertension. Cuore e circolaz. **40:** 129 (June), 1956.

In 100 hypertensive patients with clearly visible U waves, the Q-T interval, corrected for the heart rate, was prolonged in 26 per cent. The duration of U exceeded the upper normal limits of 0.20 second in 32 per cent, while the T-U interval exceeded the normal upper limit of 0.04 second in 18 per cent. The voltage of U was smaller than in normal in lead I, but greater in lead III, and in all precordial leads, especially in V_3, where it exceeded the normal limit of 0.2 mm. in 31 per cent. The voltage of T, on the contrary, was smaller than normal in all precordial leads except V_1. The magnitude of these changes was approximately proportional to the diastolic blood pressure. The mean axis of U in the frontal plane was 75°, corresponding to right axis deviation from the normal mean of 45°; the magnitude of this deviation, and also the angle between T and U, increased with the diastolic blood pressure. Most cases with deviation beyond the normal limit of 90° had marked enlargement of the heart and aorta, and in some of these the T axis was still within normal limits. The greatest voltage of U was in V_2, which corresponds to slight right axis deviation in the horozontal plane; it was to the right of the T wave maximum in 55 per cent, and of the QRS transition zone in 72 per cent. The incidence of negative U waves in precordial leads, of right axis deviation of U in the frontal plane, and of cardiac and aortic enlargement, increased with the degree of right axis deviation of T in relation to QRS. In cases with S-T depression, the U wave voltage was greater. Negative U waves in precordial leads (especially V_6) were present in 23 per cent of the cases; these cases showed a greater incidence of cardiac and aortic enlargement, but not of marked hypertension or signs of heart failure. The negative U wave was accompanied by a positive T wave in 76 per cent of the leads.

LEPESCHKIN

Aguilar, J. V. S., Perez, G. M., Castillo, A. S., and Jimenez, A. E.: Incidence of Arterial Hypertension in Cor Pulmonale. Rev. Espan. de Cardiol. **9:** 267 (July-Aug.), 1955.

In 50 cases of chronic cor pulmonale, 24 of chronic bronchopneumonia, and 14 of emphysema, the incidence of systemic arterial hypertension was 33 per cent while in 2,000 control cases (similar age groups), the incidence was only 13 per cent. The incidence of polyglobulia, low arterial oxygen saturation, or high arterial carbon dioxide was not significantly higher in cases of cor pulmonale with hypertension than in those without it.

LEPESCHKIN

Aivazian, A. V.: A Case of Pheochromocytoma of Clinical and Diagnostic Interest. Klin. Med. (Moscow) **34:** 94 (March), 1956.

In a 32-year-old woman with neurofibromatosis the blood pressure rose to 300/170 during exacerbations of headache, averaging 240/120 outside of these; oxygen insufflation of the presacral region showed a pararenal tumor. Immediately after removal of the pheochromocytoma, the blood pressure fell to 115/75 and remained at this value permanently. The transient bilateral amaurosis which appeared after operation is attributed to reduction of cerebral circulation due to sudden reduction of blood pressure.

LEPESCHKIN

Gibbons, J. E., Muller, J. C., Pryor, W. W., and Orgain, E. S.: Newer Drugs in the Treatment of Hypertension; Experience with Rauwolfia Drugs and Protoveratrine. J.A.M.A. **162:** 92 (Sept. 8), 1956.

The authors studied 58 patients with hypertensive vascular disease who were treated with rauwolfia drugs. A normal blood pressure level was achieved in 33 per cent. Doses were initially small and were gradually increased until a fall in blood pressure or unpleasant symptoms occurred. Doses were reduced when troublesome side-effects appeared. Minor side-effects were observed in 48, and severe mental illness in 4 of the patients. Among the patients with moderate and severe hypertension (mean recumbent pressures greater than 136 mm. Hg) "definite" blood pressure responses were observed in 38 per cent and blood pressure levels fell to normal in 29 per cent. The addition of protoveratrine to therapy reduced blood pressure levels further in only 15 per cent of the patients and this drug was not considered of practical value when used alone. In 19 patients veratrum preparations caused further reductions of only 2–3 mm. Hg for recumbent and standing blood pressures, although the dose was large enough to cause alarming symptoms in 2. It is felt that dose of Rauwolfia drugs should be carefully regulated and patients receiving them should be closely watched.

KITCHELL

Trout, K. W., Bertrand, C. A., and Williams, M. H.: Measurement of Blood Pressure in Obese Persons. J.A.M.A. **162:** 970 (Nov. 3), 1956.

This study points out that falsely high blood pressure readings may be obtained in people with obese upper extremities. In markedly obese individuals the true arterial blood pressure may be more accurately determined by measuring blood pressure in the forearm rather than in the upper arm. In this method the standard cuff is placed on the forearm with its midpoint 13 cm. from the olecranon process and the blood pressure determined by either auscultation or palpitation of the radial artery. It is thought that tissue composition as well as the

arm circumference may contribute to the erroneously high blood pressures recorded in obese subjects.

KITCHELL

Leiser, A. E., and Corcoran, A. C.: Antidiuretic Response to Piperoxan as a Diagnostic Test of Pheochromocytoma. J.A.M.A. **162:** 540 (Oct. 6), 1956.

It was noted that piperoxan given to patients with hypertension due to functioning pheochromocytoma caused a decrease in urine flow. This suggested that with standardized hydration the effect of piperoxan on urine flow might be useful in diagnosing these tumors. Fasting recumbent patients were given 1 L of 0.25 per cent solution sodium chloride orally and the urine was collected for 3 or 4 successive 30-minute periods. The usual test dose of piperoxan was given intravenously after the second urine collection when its effect on blood pressure was also observed. In 3 normotensive patients and 32 patients with hypertension not due to pheochromocytoma, piperoxan had a diuretic effect in that the volume of the third urine sample exceeded that of the second. In 2 patients with pheochromocytoma, and in 7 normal subjects in whom the physiology of pheochromocytoma was simulated by infusions of levarterenol (with and without a mixture of epinephrine), diuretic response to piperoxan was not observed. Antidiuresis occurred in those receiving the mixture of the 2 pressor amines. In 2 patients with pheochromocytoma, the volume of the third sample after administration of piperoxan was substantially less than that of the second urine sample. The procedure is described as a confirmatory observation in the diagnosis of functioning pheochromocytoma.

KITCHELL

Skelton, F. R.: Experimental Hypertensive Vascular Disease Accompanying Adrenal Regeneration in the Rat. Am. J. Path. **32:** 1037 (Sept.-Oct.), 1956.

An experimental study was carried out in rats to determine whether nonspecific stress produced arterial hypertension and arterial changes through an abnormal secretory response in the adrenal cortex. The study was well controlled. Twenty-four female, unilaterally-nephrectomized rats were maintained on a laboratory diet plus 1 per cent sodium chloride drinking water. Twelve rats were used as controls, and in the remainder right-sided adrenalectomy and left-sided adrenal enucleations were performed. Blood pressure determinations were made. Serum electrolyte levels were determined at varied intervals. At 7 weeks and at 14 weeks some of the experimental animals were sacrificed. Studies were made of the organs with particular attention to the condition of the vessels. The adrenal glands regenerated and showed all 3 zonas, but the zona glomerulosa was thin and composed of small cells containing lipids. Focal cortical necrosis was present in these regenerated glands. In the rat allowed 1 per cent saline drinking water, there was widespread arterial disease, in those animals with unilateral adrenalectomy and contralateral adrenal enucleation. In the kidney, there were changes of glomerulonecrosis, proliferation of glomerular epithelial cells, hemorrhage, thickening of the tubular basement membrane, and dilatation of tubules. In the cerebral tissues, there were focal infarcts and neuronal degeneration with hemorrhages. The author feels that the study supports the hypothesis that altered adrenal cortical function is important in the pathogenesis of arterial disease and hypertension, and that the stimulus for adrenal cortical hyperactivity can be endogenous, rather than always a nonspecific exogenous stress.

HARVEY

Heyman, C.: Physiologic Regulation of the Arterial Pressure and Hypertension. Acta cardiol., suppl. **6:** 8, 1956.

It is known that reflex regulation of the blood pressure is mediated through the action of baroreceptors located in the vascular wall of the sinoaortic areas. Experiments devised by the author revealed that arterial pressure does not act directly on the baroreceptors, but that the latter appear to be primarily sensitive to action tension of the arterial wall in which they are located. This tension depends on both the endovascular pressure and the biologic conditions of the vessel wall, that is the intramural tension and the resistance of the arterial wall to stretch. Increase of active tension of the arterial wall provokes, by apparently "resetting" the baroreceptor function to a lower pressure level, a marked reflex fall of arterial pressure. It is possible that a "shift" to a higher set of baroreception by a decrease of tension of the arterial wall could be the primary cause of arterial hypertension.

PICK

Govaerts, P.: Pathogenesis of Experimental Renal Hypertension. Acta cardiol., suppl. **6:** 1, 1956.

The author criticizes the method of producing arterial hypertension by means of renal vasoconstriction. In acute experiments, kidneys removed from normal as well as hypertensive dogs liberate a certain amount of renin as a result of manipulation or of surgical interference. There is thus far no evidence that the kidneys of hypertensive dogs left in situ release a pressure substance. Experiments are reported designed to clarify the problem. Blood of the vena cava was collected (50 ml.) by catheterization under local anesthesia from normal dogs with renal hypertension of variable duration and injected into a small artery of a bilaterally nephrectomized test dog. No vasoconstrictive or pressure action was recorded when blood was obtained from normal dogs or from animals that had been hypertensive for more than 35 days. On the other hand, vena caval

blood from dogs with hypertension from 3 to 31 days' duration had a local vasoconstrictive effect but failed to increase the blood pressure of the test animal. Furthermore, the blood pressure of dogs hypertensive for more than 70 days did not drop during the 3-day survival period following bilateral nephrectomy. No support was found in other experiments for the notion that renal hypertension might be due to increased reactivity to renin, epinephrine, ACTH, or DCA. The author concludes that the mechanism of experimental renal hypertension is still unexplained.

PICK

Platt, R., and Sears, H. T. N.: Reserpine in Severe Hypertension. Lancet **1:** 401 (April 14), 1956.

Prolonged, significant hypotensive effects were observed in at least 40 per cent of cases. Severe depression was observed and in 1 case suicide. Drowsiness and nasal stuffiness occurred in about half the cases. Diarrhea occurred in 4 of 54 patients. Interestingly, in 3 women, lactation was induced by the drug.

MCKUSICK

Beaven, D. W., and Murphy, E. A.: Dissecting Aneurysm During Methonium Therapy. A Report on Nine Cases Treated for Hypertension. Brit. M. J. **1:** 77 (Jan. 14), 1956.

Nine of a series of 44 hypertensive patients who came to necropsy after parenteral methonium or pentolinium therapy had dissecting aneurysms. Of the 44, 34 had malignant hypertension. Of the 34 dissecting aneurysm occurred in 6 (the other 3 patients had benign hypertension). Among 89 cases of malignant hypertension not treated with the drugs mentioned only 1 case of dissecting aneurysm occurred. Among 200 control cases of benign hypertension there were 6 with dissecting aneurysms. Therefore, use of the drugs was accompanied by an increase in the total incidence of dissecting aneurysm from 2 per cent (7/289) to 20 per cent (9/44).

Review of the literature appears to confirm the impression that dissecting aneurysm is ordinarily relatively rare in malignant hypertension. As the basis for the observed increase the authors suggest the following possibilities: prolongation of life permits time for development of this complication; fluctuation of blood pressure encourages the development of dissecting aneurysm; and these hypotensive agents have a specific biochemical effect on the aorta.

MCKUSICK

Currens, J. H., Reid, D. E., and Newell, J. L.: Hypertension Associated with Pregnancy. Incidence and Treatment, with Particular Reference to Protoveratrine. J.A.M.A. **161:** 1232 (July 28), 1956.

Although eclampsia is now infrequently seen at the Boston Lying-In-Hospital, hypertension associated with pregnancy and nonconvulsive toxemia continues to be a problem in management. In the period from 1941 to 1944 in 1 hospital the incidence of hypertension in pregnancy was 87 per 1,000; the comparable figure for the period 1951 to 1954 was 47. Improvement in prenatal care and limitation of sodium intake are considered as plausible explanations for this. Twenty-one patients were observed in whom protoveratrine was helpful in reducing or controlling the hypertension associated with pregnancy, and it is believed that both the oral and intravenous use of this drug is an improvement over the time-honored use of veratrum.

KITCHELL

Coakley, W. S., Alpert, S., and Boling, J. S.: Circulatory Responses During Anesthesia of Patients on Rauwolfia Therapy. J.A.M.A. **161:** 1143 (July 21), 1956.

Sixteen of 40 unselected hypertensive surgical patients on rauwolfia therapy showed significant hypotension and bradycardia during anesthesia. In some cases electrocardiographic tracings showed ischemic myocardial changes. The suggestion is made that patients on rauwolfia therapy who are to undergo elective surgery should not receive the drug for 2 weeks prior to planned operation. Emergency surgery on such patients may be safely carried out by using vagal-blocking drugs to prevent and treat vagal circulatory responses.

KITCHELL

PHARMACOLOGY

Ziff, M., Kibrick, A., Dresner, E., and Grigetz, H. J.: Excretion of Hydroxyproline in Patients with Rheumatic and Non-Rheumatic Diseases. J. Clin. Invest. **35:** 579 (June), 1956.

Hydroxyproline constitutes about 13 per cent of collagen, and 1 to 2 per cent of elastin, but is present in no other protein of the body. It was felt that if there were a significant deviation from normal in collagen metabolism, such changes might be reflected by an increased level of excretion of this amino acid in urine. Patients with rheumatoid arthritis, collagen diseases, and normal controls were studied. It was found that ingestion of 4 Gm. of hydroxyproline and of proline did not increase the excretion of hydroxyproline. The excretion of this amino acid, however, did rise following gelatin ingestion. There was no significant difference in the excretion of the total hydroxyproline in normal individuals or in the patients under study. Children excreted as much as 3 to 4 times the amount excreted by adults. This does not appear to be related to the absence or presence of disease, and suggests that the excretion may reflect increased quantities of a circulating and metabolically active form of collagen in the younger age group.

WAIFE

Goodall, McC., and Kirshner, N.: Effect of Cervico-Thoracic Ganglionectomy on the Adrenaline and Noradrenaline Content in the Mammalian Heart. J. Clin. Invest. **35:** 649 (June), 1956.

In the dog, the right inferior cervical ganglion, including the middle cervical ganglion when present, appears to be the group most responsible for the control of norepinephrine in the heart. This is not entirely true in the sheep, for here both the right inferior cervical, and the right thoracic ganglia influence the norepinephrine content to the greatest extent. In both dog and sheep, removal of the cardiac sympathetic ganglia had no consistent effect upon the epinephrine content of the heart.

WAIFE

Valk, A. de T., Jr., and Price, H. L.: The Chemical Estimation of Epinephrine and Norepinephrine in Human and Canine Plasma. I. A Critique of the Ethylenediamine Condensation Method. J. Clin. Invest. **35:** 837 (Aug.), 1956.

A reliable method for the estimation of epinephrine and norepinephrine in human plasma is of importance in a number of clinical situations. In this study the method of condensing epinephrine with ethylenediamine to form a fluorescent product was evaluated. The observations indicate that this method is capable of detecting amounts of epinephrine and norepinephrine of the order of 10^{-3} μg. after the addition of these hormones to plasma. However, the method is not suitable for estimating norepinephrine concentration in plasma. The specificity of the method for norepinephrine in plasma eluate is inadequate, while specificity for epinephrine is not established.

WAIFE

Tatge, W. A., Winnik, D. E., and Spencer, G. N.: Therapeutic and Toxic Effects of Enteric-coated Aminometramide. Am. J. M. Sc. **232:** 175 (Aug.), 1956.

Aminometramide is a member of a group of 6-aminouracils that have been found to produce diuresis probably by inhibiting the reabsorption of sodium and chloride in the renal tubule. Because of the occurrence of frequent gastrointestinal side effects, the drug was administered in an enteric-coated form in an effort to obviate these effects. Patients receiving the drug included 8 with portal cirrhosis, 2 with nephrosis, and 18 with congestive heart failure previously treated with mercurial diuretics. The initial dosage was 4 200-mg. tablets daily, given with or after meals; increasing doses were administered as tolerated. Six of the cirrhotic patients exhibited significant diuresis. One nephrotic patient sustained a dramatic diuresis that may have been spontaneous rather than induced. Fourteen of the cardiac group lost edema or maintained dry weight during the study. A high incidence of gastrointestinal symptoms was encountered, including anorexia, nausea, vomiting, and constipation. It is stressed that these effects were part of the test situation and may not be encountered in the therapeutic programs. It is concluded that the drug is a safe and useful addition to the diuretic armamentarium.

SHUMAN

Caccamo, L. P., Pringle, B. H., and Hissong, D. E.: A Therapeutic Evaluation of 1-Allyl-3-Ethyl-6-Aminotetrahydropyrimidinedione (Mictine), a New Oral Diuretic. Am. J. M. Sc. **232:** 289 (Sept.), 1956.

Therapeutic trials with Mictine were conducted in 16 patients with congestive heart failure or cirrhosis of the liver with edema. The majority of cases represented problems in edema management with little response to usual diuretic measures. The evaluation of results was based on a modified Kattus index. The drug was given in doses of 1.5 Gm. daily over a period of 3 days. The diuretic response was generally satisfactory as evidenced by an average daily fluid loss of 590 ml. and an average daily weight loss of about 1 lb. The diuretic index revealed that the drug was found to give appreciable responses in 68.8 per cent of the cases. Side effects consisted of nausea and vomiting in 30 per cent of the cases; in 12 per cent it was necessary to stop the drug. Repeated courses of the drug or prolonged therapy increased the tendency to produce nausea and vomiting. The results indicate that Mictine possesses substantial diuretic properties but its use is limited by side reactions.

SHUMAN

Gilbert, R., and Lyons, R. H.: Clinical Evaluation of a Digitalis Tolerance Test. Am. J. M. Sc. **232:** 144 (Aug.), 1956.

The degree of digitalization was evaluated in 20 patients using the acetylstrophanthidin method described by Lown and Levine. Three cat units of the test agent were diluted in 10 or 20 ml. of saline or dextrose in water and given intravenously at a rate of 1 ml. per minute with a direct-writing electrocardiogram operating continuously during the procedure. After 5 ml. the injection was interrupted for 5 minutes (or 3 minutes with second dilution) and then restarted if no changes were noted. If signs of digitalis toxicity developed with 1.5 cat units, the patient was considered to be overdigitalized before the test; if toxicity occurred after 3 cat units, the patient was considered adequately digitalized. Under-digitalization was present if an effect occurred after 3 or 4.5 units. The signs of digitalis intoxication included ventricular premature beats, bigeminy, prolongation of P-R interval, conversion of fibrillation to sinus rhythm and marked nausea or retching. The follow-up studies showed that the interpretation of the test was very reliable. There was 1 fatality associated with the procedure in this group. The fatal case developed ventricular tachycardia during

the test. The authors conclude that the acetylstrophanthidin test of digitalization is very accurate but quite hazardous. It is rarely needed but where indicated can give valuable and life-saving information.

SHUMAN

PHYSIOLOGY

Frank, E. D., Frank, H. A., Jacob, S., Weizel, H. A. E., Korman, H., and Fine, J.: Effect of Norepinephrine on Circulation of the Dog in Hemorrhagic Shock. Am. J. Physiol. **186:** 74 (July), 1956.

Survival and recovery were unaffected by norepinephrine infusion in unresponsive hemorrhagic shock. As the blood pressure rises after norepinephrine during shock coronary, cerebral and adrenal blood flows are increased. This was true whether or not replacement transfusion had been used. Blood flow in the kidney was reduced but that of the liver unchanged. The cardiac output was increased before transfusion but not after blood was replaced. Pressures in both atria and in the pulmonary artery were increased by norepinephrine, no matter when they were measured during hemorrhagic shock. However, the pulmonary vascular resistance was decreased.

OPPENHEIMER

Hilton, J. G., and Brown, R. V.: Blood Pressure Responses to Epinephrine in the Etherized Dog, before and after Baroreceptor Denervation. Am. J. Physiol. **186:** 71 (July), 1956.

Denervation of baroreceptors do not affect the height to which blood pressure rises after epinephrine. The duration of the hypertension is also unaffected. Denervation increased control levels and thus the height of the pressor response.

OPPENHEIMER

Jacob, S., Friedman, E. W., Levenson, S., Glotzer, P., Frank, H. A., and Fine, J. Antiadrenergic and Antihistaminic Therapy in Hemorrhagic Shock in Dog and Rat. Am. J. Physiol. **186:** 79 (July), 1956.

Premedication with dibenamine reduced the bleeding volume in dogs subjected to hemorrhagic shock. Dibenamine did not reverse intrahepatic constriction. Dibenamine dogs were less tolerant of blood loss than controls. After transfusion has become ineffective antiadrenergic or antihistaminic drugs do not reduce intrahepatic vasoconstriction nor increase survival time or rate. However, dibenamine premedication permits rats to survive a blood loss that was fatal to untreated controls.

OPPENHEIMER

Huggins, R. A., Smith, E. L., and Seibert, R. A.: Adjustments of the Circulatory System in Normal Dogs to Massive Transfusions. Am. J. Physiol. **186:** 92 (July), 1956.

After large transfusions, protein-containing plasma escapes rapidly from the circulation. When the transfusion is greater than 150 to 190 ml. per Kg. the plasma lost is in excess of that given. This would introduce an error into methods that determine blood volume based on a measurement of plasma volume. The authors express the opinion that apparent increases in hematocrit values with transfusions up to 149 ml. per Kg. are due to loss of dye from the vessels. Cells are not lost until very large transfusions produce bleeding.

OPPENHEIMER

Hackel, D. B., and Clowes, G. H. A., Jr.: Coronary Blood Flow and Myocardial Metabolism During Hypoxia in Adrenalectomized-Sympathectomized Dogs. Am. J. Physiol. **186:** 111 (July), 1956.

Coronary blood flow is increased during hypoxia. This increase does not depend necessarily on intact cardiac sympathetics or the adrenal glands. It is concluded that local metabolic changes play a primary role in the determination of coronary flow.

OPPENHEIMER

Rushmer, R. F.: Pressure-Circumference Relations of Left Ventricle. Am. J. Physiol. **186:** 115 (July) 1956.

Simultaneous measurements of left ventricular pressure and left ventricular circumference were used to produce loops on an oscilloscope. Such measurements in these experiments indicate that the external work of the heart is not necessarily related to its diastolic length. Contractility and distensibility are important parameters to be considered in cardiac adaptation.

OPPENHEIMER

Brodish, A., and Long, C. N. H.: A Technique of Cross-Circulation in the Rat Which Permits Accurate Control of Blood Volume Transfers. Yale J. Biol. & Med. **28:** 644 (June), 1956.

The authors describe a technic which allows controlled cross-circulation for use on small animals such as the laboratory rat. Their apparatus include plastic nonwettable surfaces which could accurately measure and transfuse small volumes of blood from one animal to another. The rate of transfer was about 1 ml. per minute, and at this rate 20 transfers resulted in equilibrium between the 2 circulations. Volumes as large as 100 ml. were exchanged without detriment to either animal. This technic will probably be most useful in investigating certain hematologic and endocrine problems.

ENSELBERG

Borst, H. G., McGregor, M., Whittenberger, J. L., and Berglund, E.: Influence of Pulmonary Arterial and Left Atrial Pressures on Pulmonary Vas-

cular Resistance. Circulation Research **4:** 393 (July), 1956.

Elevation of either left atrial or pulmonary artery pressure in the perfused dog's lung resulted in lowered vascular resistance. At low pressure levels, small changes in either pressure had a marked influence on resistance; the influence was progressively less in the higher ranges. The passive mechanical effects of these pressure changes, working in the same or opposite directions, may greatly modify or even outweigh the primary effects of any drug or procedure on the lung vessels. Conclusions about changes in pulmonary resistance should therefore be made cautiously, unless the measurements are made at comparable distending pressures. When this cannot be achieved, only those resistance changes opposite in direction from those to be expected on mechanical grounds may be considered due to intrinsic tone change.

AVIADO

Anzola, J., and Rushmer, R. F.: Cardiac Responses to Sympathetic Stimulation. Circulation Research **4:** 302 (May), 1956.

Cardiac function is influenced both by neural reflexes and by circulating hormones. Since the autonomic nerves to the heart exert their influence by releasing neurohormones and since the circulating hormones are released by nerve stimulation, these 2 mechanisms are frequently treated as 1. Spontaneous activity (e.g., feeding or exercise) produces effects that resemble the following responses to direct electric stimulation of sympathetic nerves to the heart of dog: tachycardia, more complete systolic ejection, and systemic hypertension. Increase in ventricular pressure following sympathetic stimulation could occur even during clamping of the aorta. These powerful sympathetic effects suggest very strongly that neural control plays an important role in the regulation of cardiac function.

AVIADO

Cobbold, A. F., and Lewis, O. J.: Blood Flow to the Knee Joint of the Dog. Effect of Heating, Cooling and Adrenaline. J. Physiol. **132:** 379 (May), 1956.

Blood flow to the knee joint as measured by a bubble flow meter varied in 6 dogs from 1.5 to 7 ml. per minute. A rise in temperature in the joint caused an increase in blood flow and a fall in temperature a decrease in flow. Epinephrine administered intra-arterially caused a constriction of joint blood vessels. These results disagree with those obtained by others utilizing plethysmography and intra-articular temperature measurements.

AVIADO

Born, G. V. R., Dawes, G. S., Mott, J. C., and Rennick, B. R.: The Constriction of the Ductus Arteriosus Caused by Oxygen and by Asphyxia in Newborn Lambs. J. Physiol. **132:** 304 (May), 1956.

In lambs delivered by cesarean section the ductus arteriosus became constricted when the arterial oxygen saturation was raised by ventilating the lungs, and dilated when it was lowered by reducing the oxygen content of the inspired air. The constriction still occurred after destruction of the brain and spinal cord, and when the systemic and pulmonary arterial pressures were stabilized. Infusion of epinephrine and norepinephrine caused constriction of the ductus arteriosus. It was concluded that either a large increase in arterial oxygen tension or the release of sympathetic amines by asphyxia may cause constriction of the ductus at birth.

AVIADO

Carlyle, A., and Grayson, J.: Factors Involved in the Control of Cerebral Blood Flow. J. Physiol. **133:** 10 (July), 1956.

Blood-flow records from the frontal lobes of sheep, goats, cats, and rabbits (measured by internal calorimetry) showed no spontaneous variations in undisturbed, lightly anesthetized animals. Resting blood-flow levels were unaffected by ganglion-blocking agents, but were reduced by intra-arterial epinephrine. Intravenous epinephrine increased blood flow, partly through the mechanical effect of the raised blood pressure, and partly through a reflex vasodilator mechanism. The evidence suggested that, in response to falling blood pressure, a fall occurred in intracerebral vascular resistance, resulting in the maintenance of relatively constant blood flow in the frontal lobes with blood pressure levels higher than about 40 mm. Hg. When blood pressure dropped below 40, there was a decline in blood flow. The preservation of relatively constant blood flow, despite changing blood pressure, is unaffected by ganglion-blocking agents and is considered to be independent of external nervous control.

AVIADO

RENAL AND ELECTROLYTE EFFECTS ON THE CIRCULATION

Barger, A. C.: The Pathogenesis of Sodium Retention in Congestive Heart Failure. Metabolism **5:** 480 (July), 1956.

Recent observations in man and dog indicate that alterations in sodium metabolism occur very early in heart disease, even before a significant change in resting venous pressure. At such a stage of cardiac incompetence there is usually a fall in renal plasma flow, and only occasionally a decrease in glomerular filtration rate. The findings in such patients are, in many respects, similar to those observed in normal individuals with imposed circulatory stress, and raise the interesting question of the possible role of pressure receptors in the reflex regulation of sodium balance. Even with minor degrees of cardiac incompetence, mild exercise further decreases the renal

plasma flow, lowers glomerular filtration rate, and is accompanied by a retention of salt and water. As the clinical condition deteriorates and resting venous pressure begins to rise, exercise produces an increasingly greater elevation of venous pressure. Such an acute elevation of venous pressure leads to sequestration of blood in the venous system and excessive filtration from the capillary bed. Since the lymphatics may, at this stage of the disease, be transporting fluid at a maximum rate, the increased filtration may not be accompanied by an increase in lymph return. With the elevation of pressure in the venous system during exercise lymph return must be further impaired, resulting in a significant decrease in "effective circulating blood volume." Such fluid dislocation further enhances sodium retention. Glomerular filtration rate may still be normal, however, even when overt failure is present, with ascites and edema. Nevertheless, the retention of sodium (introduced directly into the renal artery of dogs in failure) is convincing evidence for increased tubular reabsorption of sodium at this stage of the disease. It is important to our understanding of the pathogenesis of congestive heart failure to know whether the excessive secretion of aldosterone precedes the stage of overt failure or is apparent only in the latter stages of decompensation. With the progressive deterioration of the clinical condition of the patient and the development of anorexia and cachexia, profound alterations in renal hemodynamics ensue, further impairing the ability to excrete sodium and water.

MAXWELL

Edelman, I. S.: The Pathogenesis of Hyponatremia: Physiologic and Therapeutic Implications. Metabolism **5:** 500 (July), 1956.

The widespread clinical use of the flame photometer has made it apparent that hyponatremia is apt to occur in almost any seriously ill patient. It would appear that 3 or possibly 4 primary mechanisms result in hyponatremia: sodium depletion, potassium depletion, water excess, or possibly intracellular hypo-osmolarity due to a change in the state of intracellular anions. Hyponatremia may supervene in the presence of a normal, a low or a high total body sodium. The strategy of therapy must take into account the level of body sodium, since the administration of saline to a patient with a high body sodium and heart disease may lead to disastrous results. Demonstrable edema is a reliable guide to the quantity of body sodium; for the presence of edema does signify an increased body sodium. Conversely, dehydration and hyponatremia occur in the sodium depleted state, and respond specifically to sodium replacement therapy.

Certain infections, particularly pulmonary and meningeal tuberculosis, induce an intrinsic renal defect characterized by urinary sodium loss and hyponatremia without dehydration. Depletion of body sodium in patients with congestive failure without renal disease is thought to occur rarely, even with low sodium diets and mercurial therapy. Hyponatremia with excess body sodium, however, is not unusual in these cases. As regards serum sodium concentration and total body potassium, loss of potassium (the principal intracellular cation) may result in intracellular hypo-osmolarity and be reflected in extracellular hyponatremia. Loss of body potassium invariably parallels the fall in serum sodium concentration in the instances of postoperative hyponatremia. Administration of potassium to these subjects will raise the serum sodium concentration in a variety of instances. Primary water retention without sodium retention, but with hyponatremia, has been noted in some postoperative patients, subjects with congestive heart failure under poor control, and in patients with cirrhosis of the liver. Where edema and hyponatremia are coexistent, retention of excessive water can be assumed to be a contributing factor. Water deprivation is often an important therapeutic approach to these patients, as well as to the postoperative hyponatremic subject. A discussion of the pathways in the genesis of hyponatremia was presented, as well as therapeutic considerations in the management of patients with hyponatremia.

MAXWELL

Farber, S. J., and Soberman, R. J.: Total Body Water and Total Exchangeable Sodium in Edematous States Due to Cardiac, Renal or Hepatic Disease. J. Clin. Invest. **35:** 779 (July), 1956.

Electrolytes can be measured in extracellular fluid. In the intact man, ionic concentrations in other compartments are determined indirectly. One such assay makes use of the total exchangeable body content of electrolyte and water, a figure which may be indicative of changes occurring in the extracellular fluid as well as other body compartments. In this study, 27 miscellaneous patients served as a control for 50 patients with heart disease and edema plus 33 patients with heart disease who had previously been edematous.

Under the conditions of this study, edematous patients with heart disease have a higher ratio of body sodium to body water in their bodies than do edematous patients with hepatic or renal disease. In addition, the cardiac cases have less body water in relation to body weight than patients with hepatic or renal edema. This may indicate a probable loss of intracellular along with a simultaneous gain of extracellular water. An excess of body sodium over body water persists in patients with heart disease who have been rendered edema-free. In other words, patients with heart disease and edema, in contrast to patients with hepatic or renal edema, lose intracellular water as they gain extracellular water. Furthermore, they store excess sodium for a variable period of time after they are edema-free. Therefore, there

are different metabolic defects involving sodium and water in these 3 clinical conditions associated with edema formation.

WAIFE

Aikawa, J. K., and Fitz, R. H.: The Distribution of Hg^{203}-Labeled Mercaptomerin in Human Tissues. J. Clin. Invest. **35:** 775 (July), 1956.

The tissue distribution of the radioactive isotope of mercury, Hg^{203}, which had been administered parenterally as labeled mercaptomerin sodium, was studied in critically ill patients. Tissue analyses were performed at autopsy ranging in time from 1 to 24 days after the administration. The results indicate that following the administration of 1 dose, the concentrations of mercury in various tissues within the first 48 hours after injection were as much as 10 times higher than those observed previously in normal rabbits. The highest renal concentration of mercury was found in a patient dying of acute myocardial infarction, who had minimal arterial nephrosclerosis. An anuric subject with little functional renal tissue remaining showed the lowest concentration. It would seem that the ability of the kidney to concentrate mercury depends at least partially on the quantity and quality of the functional tissue. Although most of the values ranged between 1.2 and 9.4 μg. per Gm., the highest concentration was 70 μg. per Gm. of wet tissue.

WAIFE

Kleeman, C. R., Epstein, F. H., and White, C.: The Effect of Variations in Solute Excretion and Glomerular Filtration on Water Diuresis. J. Clin. Invest. **35:** 749 (July), 1956.

Normal subjects were put in a state of "physiological diabetes insipidus" by maintaining a sustained positive load of water resulting in maximal water diuresis associated with a minimal concentration of urinary solutes. Physiologic observations indicate that the magnitudes of the maximal urinary flow, water clearance, and minimal urinary osmolarity are directly correlated with the rate of solute excretion. The glomerular filtration rate per se, as measured by endogenous creatinine clearance, was directly correlated with the maximal urinary flow and inversely correlated with the minimal urinary osmolar concentration achieved during water diuresis. The results indicate that both glomerular filtration rate and solute load have important and statistically separable effects on the characteristics of water diuresis.

WAIFE

ROENTGENOLOGY

Amundsen, A. K., Amundsen, P., and Müller, O.: Blood Pressure and Heart Rate during Angiocardiography, Abdominal Aortography, and Arteriography of the Lower Extremities. Acta radiol. **45:** 452 (June), 1956.

Aortic or iliac artery pressures and pulses recorded during angiocardiography, aortography, or arteriography were obtained in 28 patients. In angiocardiography a fall in mean blood pressure of 8 to 16 mm. Hg occurred between 10 and 20 seconds after the injection period, continued for 30 to 40 seconds, and returned to the original figures generally in 1 minute or shortly thereafter. A slighter but earlier fall in blood pressure occurred during aortography than in arteriography. Generally, as the blood pressure fell the heart rate increased; subsequently, the rate decreased as the pressures rose toward the original values. The authors ascribe the fall in pressure to the peripheral vasodilating effect of the contrast medium.

SCHWEDEL

Reich, N. E., and Ehrlich, D. E.: Displacements of the Barium-Filled Esophagus by Cardiovascular Lesions. Dis. Chest **29:** 376 (April), 1956.

The authors stress the close anatomic relationship of the esophagus to the heart and aorta that permits important diagnostic observations concerning many cardiovascular lesions. Fluoroscopy and roentgenoscopic views should include posteroanterior, right and left anterior oblique, and right lateral views. They review the pressure defects and displacements resulting from the various congenital abnormalities of the heart and great vessels as well as those observed in rheumatic heart disease, syphilitic aortitis, atherosclerosis of the aorta, and dissecting aneurysms.

MAXWELL

Kenney, L. J., and Eyler, W. R.: Preoperative Diagnosis of Sequestration of the Lung by Aortography. J.A.M.A. **160:** 1464 (April 28), 1956.

The diagnosis of pulmonary sequestration is always tentative until an exploratory thoracotomy confirms the preoperative impression. In the case reported in this article, retrograde aortography established an exact preoperative diagnosis by demonstration of the anomalous artery from the aorta, branching in the sequestrated lung. It is suggested that a retrograde aortogram be made when this diagnosis is considered.

KITCHELL

OTHER SUBJECTS

Morris, A. J., Chamovitz, R., Catanzaro, F. J., and Rammelkamp, C. H., Jr.: Prevention of Rheumatic Fever by Treatment of Previous Streptococcic Infections. J.A.M.A. **160:** 114 (Jan. 14), 1956. Abstracted, Circulation **15:** 574 (April), 1957.

Rifkin, H.: The Kimmelstiel-Wilson Syndrome: Clinical Aspects. J. Mt. Sinai Hosp. **23:** 674, (Sept.-Oct.), 1956. Abstracted, Circulation **15:** 854 (June), 1957.

Wineburg, E. N.: The Hospital Visitor: A Study of Responses of Cardiac Patients to Visiting Hours. Cardiologia **29:** 332 (No. 5), 1956.

Thirty-two patients hospitalized for organic or functional cardiac disorders were selected to study the influence of visitors upon the momentary state of the disease. Central and peripheral pulse rates, blood pressures, rates of respiration and temperatures were noted on visiting days and compared with corresponding data on control days. All these functions showed a small increase after visiting hours but only the blood pressure elevation was statistically significant. Women were more prone to such changes than men and the reaction of hypertensive patients was more marked than in other conditions. On direct questioning most patients expressed a desire for visiting time shorter than 1½ hours. They felt poorer and more tired after the visit but all were happy to have visitors. Encouraging remarks from the visitors appeared to be beneficial to the patient.

PICK

DuBois, E. L.: Systemic Lupus Erythematosus: Recent Advances in Its Diagnosis and Treatment. Ann. Int. Med. **45:** 163 (Aug.), 1956.

The author has reviewed his experiences with the diagnosis and treatment of 163 cases of systemic lupus erythematosus over a 6-year period at the Los Angeles County General Hospital. The apparently increasing incidence of this disease is a function of the increased sensitivity and more frequent usage of the L.E. cell test and the broader concept of systemic lupus erythematosus, which is a chronic disease resembling rheumatoid arthritis. Simultaneous L.E. cell studies were performed on 44 patients with systemic lupus erythematosus by 4 different methods, utilizing 2 concentrations of heparin as an anticoagulant, a clotted method, and the recent Snapper ring technic. In 10 cases the clotted method was the only positive test; in 4 the ring technic was the only positive test, and in 2 cases the heparinized specimen was the only positive one. With increasing amounts of heparin fewer L.E cells were found. It is advisable that at least 3 different types of L.E. cell tests be performed to screen a suspected case adequately. Despite these refinements, L.E. cells are not found in all patients with the disease.

A study of the natural history of a large series of cases gives us the best concept of the course of the illness. Of this series, 38.6 per cent have had spontaneous remissions prior to any special therapy. Certainly many of the treated patients would have had remissions without therapy. Six per cent of the series had at least 2 remissions, and 16 per cent 3 or more. This makes evaluation of therapy difficult. Antimalarial drugs have a definite place in the treatment of systemic lupus erythematosus, particularly in the milder cases. Their effect on the cutaneous lesions is almost specific. The arthritis is also greatly benefited. Their synergistic use with steroids often reduces the steroid dose and may permit one to stop steroid treatment entirely. Eighty per cent of the milder cases are benefited by antimalarials alone. Steroid therapy is still the mainstay of treatment in the acutely ill patient, and benefits 90 per cent of the patients so treated. Nitrogen mustard has been shown to ameliorate the nephropathy of systemic lupus erythematosus, particularly in the more edematous patients. The lives of these patients are prolonged by this form of therapy. The median duration of life of 59 untreated or inadequately treated patients at this hospital was 24 months. In the present series of 138 adequately treated patients ill for 24 months or more, less than 10 per cent have died. This difference is significant.

WENDKOS

Kryle, L. S., Calvelli, E., Bonham, D. T., and Kupperman, H. S.: Clinical Studies on the Use of Parenteral Trypsin and Chymotrypsin in Peripheral Vascular Disease. Angiology **7:** 287 (June), 1956.

Seventy-nine patients with a variety of circulatory defects were treated with intravenous and intramuscular trypsin and with chymotrypsin. The authors state that although thrombi were not dissolved with these drugs, subsidence of the inflammatory process was accelerated.

WESSLER

Wakim, K. G., and Fleisher, G. A: The Effect of Experimental Cerebral Infarction on Transaminase Activity in Serum, Cerebrospinal Fluid and Infarcted Tissue. Proc. Staff Meet., Mayo Clin. **31:** 377 (June), 1956.

The production of experimental cerebral infarction in dogs by injection of vinyl acetate into the isolated internal carotid artery in the neck under aseptic surgical technic invariably leads to marked increase in the activity of glutamic oxalacetic transaminase in the cerebrospinal fluid, which reaches a peak within 100 hours after infarction. Thereafter the increase in transaminase activity in the cerebrospinal fluid gradually decreases but still remains above preinfarction level 15 days after infarction. The augmentation of transaminase activity in the cerebrospinal fluid is proportional to the severity and extent of cerebral infarction. Usually the transaminase activity in the serum also increases, but the increase is not as marked as in the cerebrospinal fluid, does not always occur, is not proportional to the severity and extent of the infarct, and does not appear as soon as it does in the cerebrospinal fluid after infarction. The determination of transaminase activity in the cerebrospinal fluid may serve as a good test for the diagnosis of cerebral tissue damage.

SIMON

Baer, S.: Varied Manifestations of Dissecting Aneurysm of the Aorta. J.A.M.A. **161:** 689 (June 23), 1956.

Because of the tremendous advances occurring in the field of cardiovascular surgery, the diagnosis of dissecting aneurysm of the aorta while the patient is still living is quite important, as it is reasonable to expect many of these cases may be amenable to surgical correction. In this series of 86 patients found at autopsy to have this condition, 34 were correctly diagnosed ante mortem. Remarkably enough, pain, which was excruciating in some patients, was absent in 42 of the 86. The symptom complex resulting from dissecting aneurysm of the aorta may be described as cardiovascular, pulmonary, abdominal, renal or neurologic, depending on the dominant group of symptoms and signs. Dyspnea and neurologic disturbances are important diagnostically. A diastolic aortic bruit, bizarre neurologic signs, and hemothorax on the left were valuable diagnostic signs. It is interesting to note that 1 case in this series occurred between the ages of 20 and 29 although the majority of cases occurred between the ages of 50 and 69, and 67 per cent of the cases were noted in men.

KITCHELL

Stallworth, J. M., and Jeffords, J. V.: Clinical Effects of Azapetine (Ilidar) on Peripheral Arterial Disease. J.A.M.A. **161:** 840 (June 30), 1956.

Azapetine is one of a group of adrenergic drugs that unmasks a latent dilator response to circulating epinephrine in skeletal muscle and skin, converting a constrictor response to one of vasodilatation. During 18 months 52 patients with diagnosed peripheral arterial disease have been treated with this new drug. In addition, 10 of these patients were given azapetine intravenously as a therapeutic trial prior to oral administration of the drug. Sixty-two evaluations, therefore, were made among 52 patients. Of 18 patients receiving 75 mg. of azapetine daily, in divided doses, 5 were classified as showing poor results, 2 fair, and the remaining 11 patients (61 per cent) showed a good response. In the group of 31 patients receiving 100 mg. daily only 5 patients responded poorly; these 5 were made up of one case of Raynaud's Disease with far advanced scleroderma, and the remainder advanced arteriosclerotic obliterative disease. In group 3, 9 patients were given a diagnostic trial of intravenously administered azapetine. Of the 9, only 3 patients presented no beneficial change in amplitude of oscillometric recordings (one of these later responded to azapetine orally). In group 4, all of whom were in acute distress from vasospastic disease or acute occlusive disease with associated vasospasm, azepetine was given therapeutically intravenously to 4 patients. Two cases of peripheral emboli were treated with good results. Remarkably good results were obtained in a patient who suffered from phlegmasia cerulea dolens and who suffered a pulmonary embolus for which she was admitted to the hospital. One patient died 45 minutes after intravenous administration of azapetine. It was impossible to show any direct possible harmful effect of azapetine in this case, but it is reported for further evaluation when more clinical data become available. Azapetine appears to be a very potent vasodilator with a high degree of effectiveness in purely vasospastic peripheral circulatory disorders. It is also a useful adjunct in the treatment of a basospastic element in arteriosclerotic obliterative disease. The pattern of response to azapetine administered orally or intravenously correlated closely with the clinical response following sympathectomy in the same group of patients.

KITCHELL

Landau, J., Nelken, E., and Davis, E.: Hereditary Hemorrhagic Telangiectasia with Retinal and Conjunctival Lesions. Lancet **2:** 230 (Aug. 2), 1956.

The authors describe and picture telangiectases of the bulbar conjunctiva and tortuosity with varicosity of the retinal veins. They suggest that slit-lamp examination of the conjunctival vessels may be helpful diagnostically in suspected Rendu-Osler-Weber syndrome.

McKUSICK

Fountain, J. R., and Taverner, D.: Gangrene of Three Limbs Resulting from Venous Occlusion. Ann. Int. Med. **44:** 549 (Mar.), 1956.

Gangrene of the limbs resulting from venous occlusion without arterial obstruction is extremely rare. The case reported in this communication represents the thirty first instance of this condition. She was a housewife, age 42 years, who was admitted to St. James's Hospital in Leeds, England, on December 6, 1953, in status asthmaticus of 36 hours' duration. She gave a history of recurrent attacks of bronchial asthma for 15 years. She had no other complaints, and gave no history of serious illness in the past. Nine days after admission, she complained of pain in the right calf, which was swollen and tender. Her temperature rose to 100.2 F. Thrombophlebitis was diagnosed, and treatment with an anticoagulant (Tromexan) and penicillin was started. Two days later the swelling had increased, and marked pitting edema was present up to the midthigh and down over the dorsum of the right foot. The left calf was now also tender, and edema was present below the knee. Both legs and feet were warm and no color changes were visible. The femoral and popliteal pulses were present and equal, but pulsation of the dorsalis pedis arteries was not detected, probably because the edema obscured it. Twenty-three days after admission considerable improvement had resulted. Anticoagulant therapy was stopped 2 days later. Twenty-

six days after admission the temperature rose to 101.2 F. and the pain and edema recurred, appearing first in the left calf and the following day in the right calf. The edema rapidly increased, involving the whole of the right lower limb and extending to the midthigh on the left side. Edema also appeared over the lower abdominal wall and sacrum, and a few distended veins were seen over the lower abdomen. Heparin and, later, Tromexan were given, with satisfactory effects on blood coagulation. Penicillin, and, later, Aureomycin were also prescribed but with little effect on the pyrexia. Forty-six days after admission, the patient developed an acute attack of pain over the right lower chest and a slight hemoptysis occurred. The temperature was 102 F., and a pleural rub was audible at the right lung base. Pulmonary infarction was diagnosed. The edema of the lower limbs persisted, and both feet were intensely cyanotic. The feet were still warm and the popliteal pulse was present in the left side, but other pulses were not palpable in the lower limbs because of the massive edema. The discoloration rapidly spread up the limbs and lines of demarcation became apparent on the right side of the midcalf region, and on the left side at the junction of the middle and lower thirds of the thigh. Forty-eight days after admission the right forearm and hand became edematous and blue. A sharp line of demarcation appeared 3 inches below the right elbow joint. However, the edema persisted, the temperature remained elevated, severe pain continued, and large bullae appeared over the affected parts. The discoloration of the affected limbs remained unchanged and the feet and right hand became cold and gangrenous. Hematuria and hemoptysis of mild degree, with a progressive anemia, were observed terminally, and the patient died 61 days after admission. At the autopsy it was observed that both femoral and iliac veins were thrombosed up to the junction of the common iliac veins. The inferior vena cava and portal veins were free of thrombus. Small veins around the pelvic organs were thrombosed and some of the pelvic muscles appeared soft and partly necrotic. Numerous small veins in the lower limbs were examined and found to be thrombosed. The femoral arteries were followed throughout their course and neither they nor the tibial arteries showed evidence of thrombus formation. The right radial and ulnar arteries were examined at the wrist and found to be free of thrombus. The brachial vein and the proximal ends of the ulnar and radial veins did not show any thrombosis, although examination of the veins in the forearm was rendered difficult by considerable adipose tissue, edema and gangrene. Microscopic examination revealed hypertrophy of the bronchial muscle and emphysema. Thrombi of varying ages were seen in the branches of the pulmonary artery, some recent and others organized. Congestion and edema of the lungs were widespread, and part of the right lung was infarcted. Pelvic veins were found to contain recent and organized thrombi, but arteries and arterioles were patent. A few lymphocytes were seen scattered in the vessel walls, but no real evidence of inflammation was to be seen. A few fibers of pelvic muscle were pale staining and probably in an early stage of necrosis. A specimen of the left femoral vein showed the lumen to be filled by thrombus, the outer part of which was organized and partly recanalized. Some groups of lymphocytes were seen in the organized thrombus, but there was no evidence of inflammation.

WENDKOS

Villamil, M. F., and Beherán, H.: Treatment of Phlebothrombosis and Its Sequelae with Intra-Arterial Trypsin. Angiology **7:** 179 (Apr.), 1956.

Intraarterial trypsin combined with procaine and Benadryl was used in the management of 7 patients with acute venous thrombosis, and in 8 patients with evidence of chronic venous insufficiency. The author believes that in acute venous thrombosis pain and edema subsided quickly and that the duration of the illness was shortened. Among the patients with chronic venous insufficiency, there was little improvement in edema, moderate improvement in secondary skin changes and marked improvement in the healing of ulcers. In 1 patient with acute venous thrombosis and an allergic background, an anaphylactic-like reaction required the cessation of therapy.

WESSLER

Rogers, J. V., and Roberto, A. E.: Circumscribed Pulmonary Lesions in Periarteritis Nodosa and Wagener's Granulomatosis. Am. J. Roentgenol. **76:** 88 (July), 1956.

The authors state that in classical periarteritis nodosa the lungs are involved in about one fourth of the cases. Hilar enlargement, nodulation, perivascular and parenchymal infiltrations, often extending bilaterally from the hili giving a bat wing appearance are frequently noted. Cardiac enlargement combined with lung changes often simulates pulmonary congestions, uremia, or allergy.

Wegener's granulomatosis considered by some to be a respiratory-renal subtype of periarteritis, is characterized by necrotizing granulomatous lesions in the lung or bronchial tree, generalized necrotizing vasculitis, and focal glomerulonephritis. The pulmonary lesions are usually circumscribed and often undergo cavitation.

Three cases are reported, 1 with vascular lesions in the dura, lungs, and spleen, plus subacute and chronic glomerulonephritis and interstitial myocarditis; another with a solitary circumscribed pulmonary lesion removed at surgery, attributed to vasculitis; a third unproved case with a receding

pulmonary density in a man clinically suspected to have periarteritis.

SCHWEDEL

Jungmann, H., and Erdmann, W. D.: The Pulse Wave in Sclerotic Arteries. Ztschr. Kreislaufforsch. **45:** 252 (Apr.), 1956.

In the presence of arteriosclerosis the carotid pulse is characterized by a rectilinear diastolic descent, the femoral pulse by a longer ascent to the apex, the disappearance of the dicrotic wave and the appearance of an incisura. The same changes could be reproduced in dogs by the insertion of a stiff plastic tube into the aorta, and are therefore attributed to decreased elasticity of the aorta. The pulse velocity in the abdominal aorta is usually increased in arteriosclerosis if no obstruction develops, while the velocity in the extremities is usually decreased.

LEPESCHKIN

Gottsegen, G., and Szam, I.: A Peculiar Vascular Disease Leading to Closure of the Brachiocephalic Arteries. Ztschr. Kreislaufforsch. **45:** 196 (Mar.), 1956.

A 29-year-old woman who complained of paresthesias in the hands and marked orthostatic dizziness showed absence of pulsation in the arteries of both arms, reduced pulsation of the left carotid and the ocular fundus arteries, but increased pulsation in the leg arteries, where the systolic pressure reached 280 mm. The hypertension was attributed to partial obliteration of the carotid sinus. Of the 24 cases of this "pulseless disease" reported in the literature, 22 were women and less than 45 years old. The designation "epiaortic arteritis" is proposed for the syndrome.

LEPESCHKIN

Hansen, P. F., and Thorn, N. A.: Viscosity of the Blood in vitro at Various Temperatures in 26 Patients with Raynaud's Phenomenon. Am. J. M. Sc. **231:** 665 (June), 1956.

The blood viscosity of 26 patients with Raynaud's phenomenon was measured over a temperature range of 5 to 40 C. Comparison of the results with those obtained in a control group revealed no abnormalities in the patients with 1 exception. The latter was a patient with chronic lymphatic leukemia whose blood formed a solid mass when cooled below 26 C. Based on these findings the authors conclude that reversible cold embolism caused by cold hemagglutination or cryoglobulins is a rare causal factor in the mechanism of Raynaud's phenomenon. The measurement of the viscosity of blood in vitro at low temperature is a simple procedure that will detect both types of cold embolism. This test should be included in the examination of patients with this disorder.

SHUMAN

Gaskell, P.: The Rate of Blood Flow in the Foot and Calf before and after Reconstruction by Arterial Grafting of an Occluded Main Artery to the Lower Limb. Clin. Sci. **15:** 259 (May), 1956.

Eleven patients with arterial occlusion in a lower limb were studied plethysmographically before and after replacement of the occluded segment by arterial homograft. The degree of arterial occlusion was best indicated by measurement of the reactive hyperemia blood flow in the foot or calf, and by a reduced arterial cuff occlusion pressure. Maximum resting blood flow was a poor index of the grade of arterial insufficiency, and even gave parodoxic results. The simplest test was the cuff occlusion pressure that served as a reliable index of arterial occlusion.

Postoperative tests indicated at least some success in restoring adequate blood flow. In some cases there was actually an increase in flow through the calf, which subsided in a few weeks. Late follow-ups showed maintenance of adequate blood flow in 3 cases, improvement in 2, and redevelopment of occlusion in the remaining 6.

ENSELBERG

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NEW OFFICERS OF ASSOCIATION AND COUNCILS ELECTED BY HEART ASSOCIATION

Francis L. Chamberlain, M.D., Associate Clinical Professor of Medicine, University of California School of Medicine, San Francisco, was chosen as President-elect of the American Heart Association by the national Assembly at the Annual Meeting in Chicago last October. At the same meeting, Robert W. Wilkins, M.D., Professor of Medicine, Boston University School of Medicine, was installed as President for the 1957–58 term.

Retiring President Edgar V. Allen, M.D., Senior Consultant in Medicine, Mayo Clinic, Rochester, Minn., became Chairman of the Heart Association's Central Committee for Medical and Community Program.

Newly elected as Vice Presidents of the Association were: George E. Burch, M.D., New Orleans; A. Carlton Ernstene, M.D., Cleveland; Kenneth G. Kohlstaedt, M.D., Indianapolis; Frank L. Mechem, Seattle; Oglesby Paul, M.D., Chicago; and Louis E. Viko, M.D., Salt Lake City.

Continuing as Vice Presidents are: Irving B. Hexter, Cleveland; Louis E. Martin, M.D., Los Angeles; and Sylvester L. Weaver, Jr., New York. Berkeley D. Johnson, New York, was re-elected Treasurer.

The Association's Councils have chosen the following officers:

Council on Basic Science: James V. Warren, M.D., Durham, N. C., Chairman; Earl Wood, M.D., Rochester, Minn., Vice-Chairman; Lysle Peterson, M.D., Philadelphia, Secretary.

Council on Circulation: William Goldring, M.D., New York, Chairman; Herbert Chasis, M.D., New York, Vice-Chairman; Grace M. Roth, Ph.D., Rochester, Minn., Secretary-Treasurer.

Council on Clinical Cardiology: William P. Thompson, M.D., Los Angeles, Chairman; Hugh Hussey, M.D., Washington, D.C., Vice-Chairman; Francis F. Rosenbaum, M.D., Milwaukee, Secretary.

Council on Cardiovascular Surgery: Robert Gross, M.D., Boston, Chairman; John H. Gibbon, Jr., M.D., Philadelphia, Vice-Chairman; William W. L. Glenn, M.D., New Haven, Conn., Secretary.

Council for High Blood Pressure: Officers scheduled for election at the Council's Annual Meeting in Cleveland, November 22–23.

Council on Community Service and Education: Oglesby Paul, M.D., Chicago, Chairman; Herbert Pollack, M.D., New York, Vice-Chairman.

Council on Rheumatic Fever and Congenital Heart Disease: Currier McEwen, M.D., New York, Chairman; Ruth Whittemore, M.D., New Haven, Conn., Vice-Chairman.

CATALOG OF PROFESSIONAL MATERIALS AVAILABLE

A revised, comprehensive catalog, "Publications and Teaching Aids for Physicians," is available from the national office of the American Heart Association or from local Heart Associations.

Included in the catalog are brief descriptions of each item and its price. A foreword expresses the hope that the professional materials listed in the catalog will "aid the physician in continuing his medical education in cardiovascular disease and in exerting leadership in the heart movement."

The catalog points out that the Heart Associations' educational programs include scientific sessions, postgraduate courses, teaching days, and annual symposia. Among the teaching aids are monographs, pamphlets, films, slides, recordings, and other audiovisual materials. The Association's professional journals,

a vital part of this program, are described in the catalog, which notes that they carry monthly summaries of progress in cardiology that is of practical interest to the physician.

"Participation in his local Heart Association places the physician in a strategic position to assure that the development of the heart program proceeds along approved medical and scientific lines," the Foreword states. "It also enables him to see to it that the steady flow of new knowledge about the cardiovascular system and its disorders becomes, through application by the family physician, of direct benefit to the heart patient."

PULMONARY CIRCULATION CONFERENCE SCHEDULED

Physicians and scientists are invited to attend a conference on "The Pulmonary Circulation," sponsored by the Chicago Heart Association at the Palmer House, Chicago, March 20–22, 1958.

Introductory sessions will be devoted to the physiology, anatomy and pathology of the pulmonary circulation, with special emphasis on methods of clinical study. Other sessions will cover the pulmonary circulation in congenital heart disease, primary lung disease and in acquired heart disease. Wright Adams, M.D., Department of Medicine, University of Chicago, Chicago 37, Ill., is chairman of the Symposium and Planning Committee.

DR. SCHMIDT NAMED EDITOR OF CIRCULATION RESEARCH

Carl F. Schmidt, M.D., Professor of Pharmacology at the University of Pennsylvania Medical School, was named editor of *Circulation Research* when Carl J. Wiggers, M.D., asked to be relieved of his duties as editor in October. *Circulation Research* has been under Dr. Wiggers' editorship since its inception in March, 1953, and owes its present high level of accomplishment to his guidance.

Dr. Schmidt received his medical degree at the University of Pennsylvania in 1918 and has since served its Medical School in various capacities. He is widely known as a lecturer and has served the United States government on medical missions throughout the world. Manuscripts may be addressed to Dr. Schmidt at the University of Pennsylvania School of Medicine, Laboratory of Pharmacology, Philadelphia 4, Pa.

MEETINGS CALENDAR

January 24, 1958: American Federation for Clinical Research, Southern Section, New Orleans. Kenneth R. Crispell, M.D., Department of Internal Medicine, University Hospital, Charlottesville, Va.

January 29–30: American Federation for Clinical Research, Western Section, Carmel, California. Monte A. Greer, M.D., University of Oregon Medical School, Portland, Ore.

February 12–14: American Academy of Occupational Medicine, New York. Leonard J. Goldwater, M.D., 600 West 168th Street, New York, N. Y.

March 9–14: International College of Surgeons, 11th Biennial Congress, Los Angeles. Karl A. Meyer, M.D., 1516 Lake Shore Drive, Chicago 10, Ill.

March 10–13: Southeastern Surgical Congress, Baltimore. B. T. Beasley, M.D., 45 Edgewood Avenue, S.E., Atlanta 3, Ga.

March 20–22: Chicago Heart Association, Conference on Pulmonary Circulation, Palmer House, Chicago. Wright Adams, M.D., Department of Medicine, University of Chicago, Chicago 37, Ill.

April 24–26: Fifth International Congress of Internal Medicine, Philadelphia. E. R. Loveland, 4200 Pine Street, Philadelphia, Pa.

ABROAD

January 7–10: Third International Symposium on Radioactive Isotopes in Clinical Application and Research, Bad Gastein, Austria. The Second Medical Clinic, Vienna University, Vienna, Austria.

January 21–February 14: International Union of Biochemistry, General Assembly, Vienna, Austria. Prof. R. H. J. Thompson, Department of Chemical Pathology, Guy's Hospital Medical School, London, S.E. 1, England.

April 16–19: International Academy of Legal Medicine and of Social Medicine, 50th International Congress, Madrid. Prof. B. Piga, Professor of Legal Medicine, Madrid University, Madrid, Spain.

July 15–21: Medical Women's International Association, 8th Congress, London. J. Aitken, M.D., 30A Acacia Road, London, N.W. 8, England.

September 14–21: Third World Congress of Cardiology, Brussels. Dr. Van Dooren, 80 Rue Mercelis, Brussels, Belgium.

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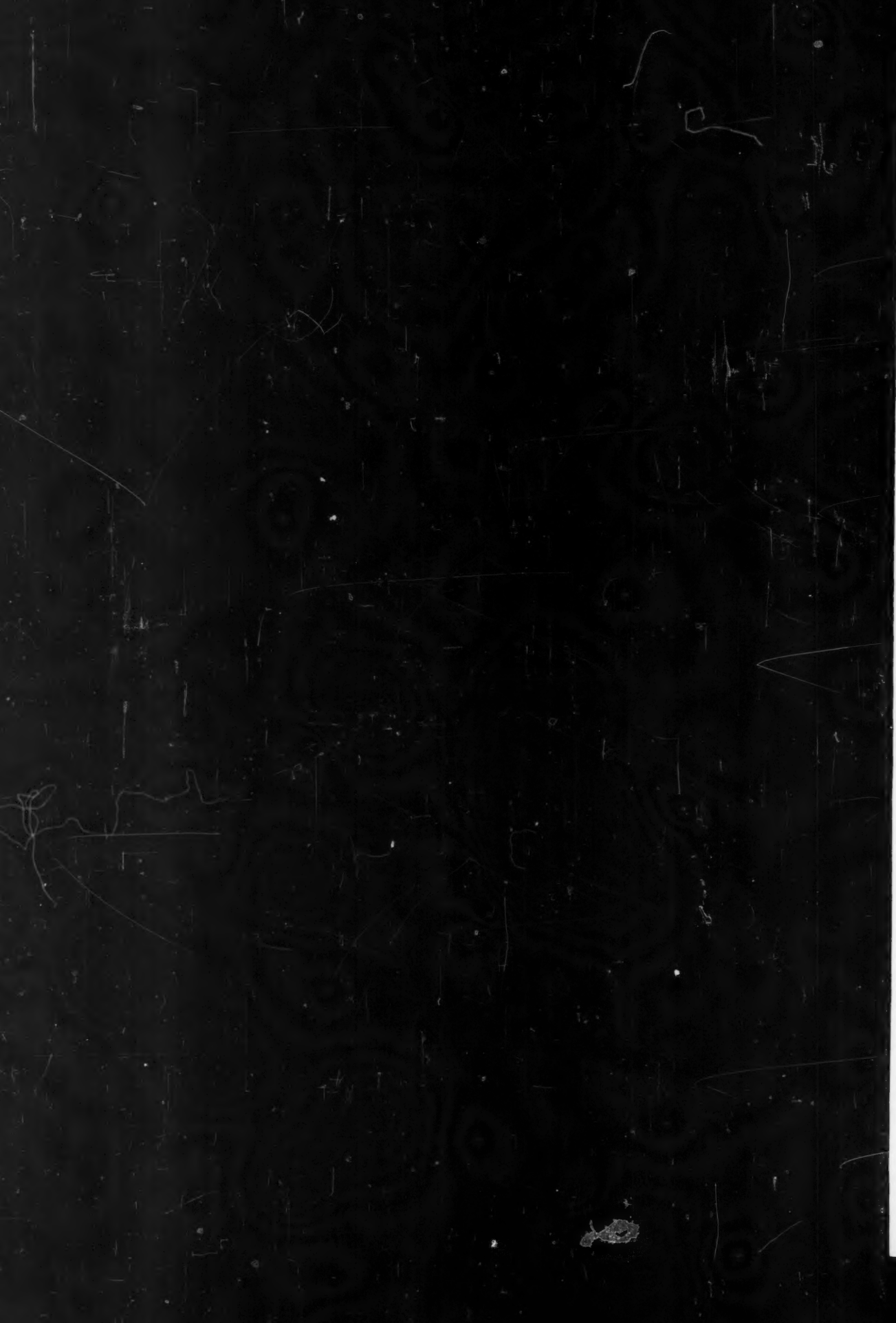

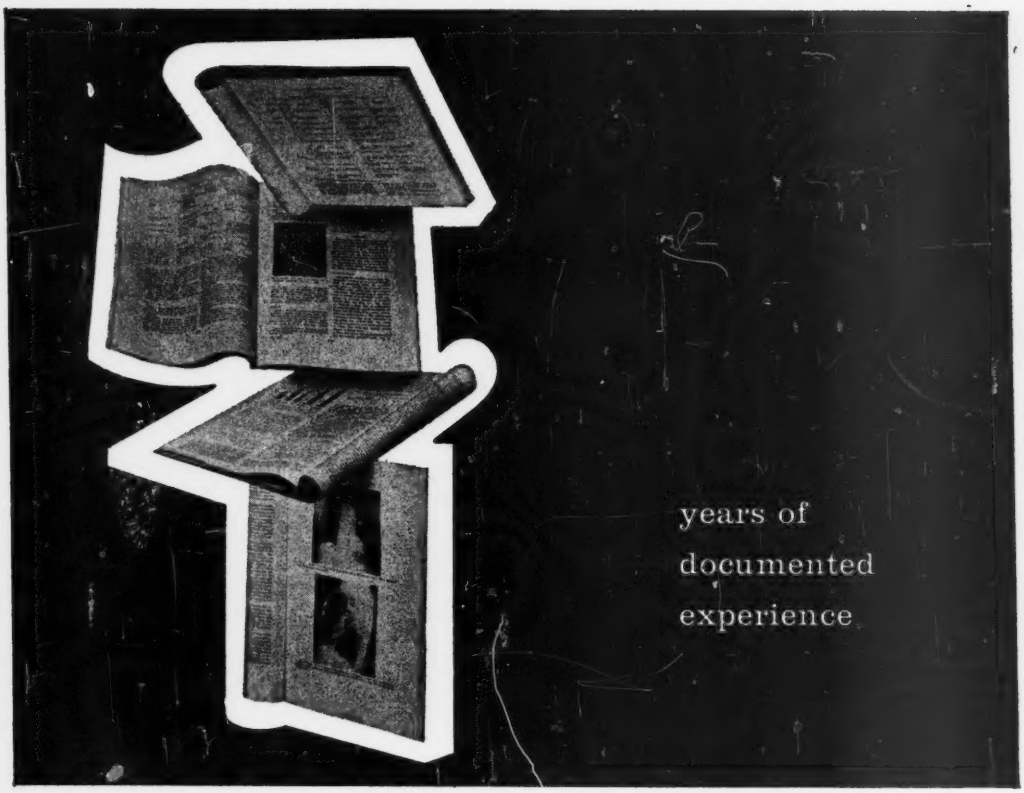

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